PSJ2 Exh 99


PAIN MANAGEMENT SUMMIT
Focus on Opioid Therapy
December 14–15, 2012
Philadelphia, PA
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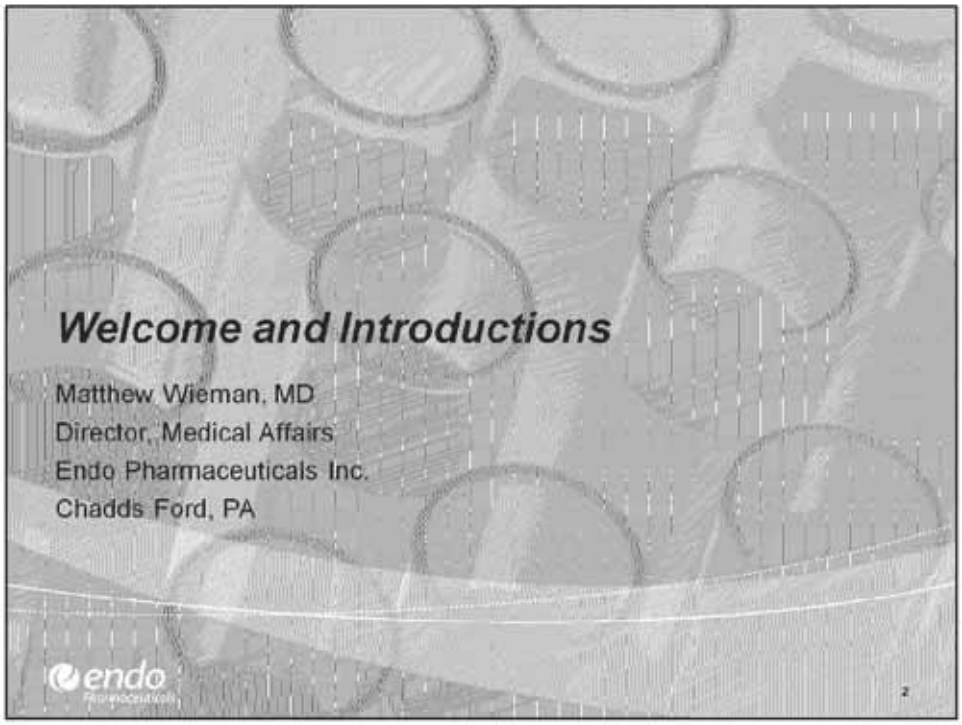

AGENDA

8:00 AM – 8:15 AM	Welcome and introductions	Matt Wieman
8:15 AM – 8:30 AM	Meeting objectives	Howard Smith - Chair
8:30 AM – 9:30 AM	Opioid therapy for chronic moderate to severe pain management: best practices	John Peppin
9:30 AM – 10:15 AM	Oxymorphone pharmacology	Chris Herndon
10:15 AM – 10:30 AM	Break	
10:30 AM – 12:00 PM	Oxymorphone continuum of care	Howard Smith
Noon – 12:45 PM	LUNCH	
12:45 PM – 1:45 PM	Effect of reformulation of OPANA® ER on abuse of the product: early experience from surveillance data through 3Q2012	Neil Shusterman
1:45 PM – 2:45 PM	Oxymorphone in pain management	Matt Wieman Rob Gatley
2:45 PM – 3:00 PM	Closing statements	Matt Wieman Howard Smith
3:00 PM	Departures	

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Meeting Objectives

- Best practices for opioid therapy in chronic pain management
  - Risks and challenges associated with the use of opioids
  - Barriers to the successful use of opioids
  - Practitioner knowledge and training gaps
  - Patient knowledge gaps
  - Risk mitigation strategies
  - Best practices development
- Oxymorphone molecule for chronic pain management
  - Uniqueness of the molecule as a therapeutic agent
  - Place in pain management armamentarium and continuum of pain care
  - Knowledge/informational/clinical study gaps regarding the molecule

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Challenges Associated With Chronic Opioid Therapy

- Opioid prescribing for pain of noncancer origin is increasing
  - Concomitant increased opioid overdose and mortality[1]
- 2007, opioids implicated in >11,000 fatal overdoses[1]
  - 17,000 deaths from NSAIDs[2,3]
- Some states have enacted legislation to
  - Limit opioid dosing
  - Improve patient screening and monitoring
  - Encourage appropriate follow-up of aberrant drug-related behavior[4]
- Data not yet available to show whether these measures will work
- Can implementation on evidence-based "best practices" mitigate abuse and misuse without creating barriers to care?

1. Paulozzi et al. Pain Med. 2011;12(5):747-754
2. Gurkirpal. Am J Med 1998;105:531-36
3. Wolfe et al. NEJM. 1999;340:1888-1899
4. AMDG. Available at: http://www.agencymeddirectors.wa.gov/Files/OpioidGdline.pdf

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Physician Knowledge

- Physicians not confident in their knowledge of opioid abuse, misuse, addiction, diversion
  - Physician survey: 70% concerned about facilitating abuse or addiction[1]
  - Retrospective analysis UDM program
    - 55% of physicians continued to prescribe[2]

1. Wenghofer et al. Can Fam Physician. 2011;57:324-332
2. Gupta et al. Pain Physician. 2011;14:383-389

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Physician Training

- Most undergraduate medical curricula include surprisingly little training in pain management, opioids, addiction, end of life, palliative medicine, and giving bad news is poorly addressed[1,2]
  - <30% of US medical schools require opioid instruction[1]
  - <10% require instruction about abuse and addiction
  - <10% in palliative medicine/EOL
  - Mean number of hours in pain management was 11.1 (range, 1–31 hours)[1]
    - Veterinary schools devoted 5-fold more hours[2]

1. Mezei et al. J Pain. 2011;12(12):1199-1208
2. Watt-Watson. Pain Res Manag. 2009;14(6):429-444

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What Is Fundamental Knowledge for Responsible Opioid Prescribing?

- Complexity of chronic pain
  - Requires "nonlinear" wholistic thinking
- Clinical pharmacology of opioids
  - Selecting appropriate opioid molecule
  - Selecting appropriate dose and treatment duration
  - Adjuvant and opioid-sparing therapies
- Factors contributing to attractiveness for abuse
  - Molecule-based vs formulation-based attractiveness
  - Benefits and limitations of abuse-deterrent formulations
  - Appropriate/inappropriate use of abuse-deterrent formulations
- Detection and management of aberrant drug behavior
  - Patient COMPLETE history and physical examination
    - Includes psychological evaluation, comorbidities, other medications etc…
  - Patient opioid treatment agreement

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Risk Evaluation and Mitigation Strategies

- Risk Evaluation and Mitigation Strategies (REMS) for long-acting/extended-release (ER/LA) opioids first released in 2009; final version in 2012
  - REMS is just a RISKMAP[1]
  - Never been shown to reduce abuse, misuse, diversion, or overdose deaths
- Focus is on education to ensure that prescribers understand
  - Opioid pharmacology
  - Risks and benefits of opioid therapy
  - Proper patient selection and monitoring
  - How to recognize opioid misuse, abuse, and addiction

1. Peppin et al. Issues in Law and Medicine. 2011; 27: 91-119

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Risk Evaluation and Mitigation Strategies

- Opioid ER/LA REMS are voluntary: physicians not required to have special training before prescribing ER/LA opioids
  - No REMS for hydrocodone or oxycodone combination products
- Survey of 259 physicians[1] found that 48% would comply
  - Only 10%–18% claimed that they would discontinue prescribing opioids if required to comply with REMS
  - However, legislation has affected numbers of physicians who prescribe, empirically eg, HB1 in Kentucky

1. Slavin et al. J Opioid Manag. 2011;7(2):109-115

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Prescription Drug Monitoring Programs

- Prescription Drug Monitoring Programs (PDMPs) gather data on
  - Inappropriate use of prescription drugs
  - Acquisition of controlled substances by "doctor shopping"
  - Initiatives undertaken by regulatory, health, and law enforcement agencies
- PDMPs never been shown to achieve the above goals
  - KASPER in Kentucky has shown an increase in prescribing of opioids since its inception

http://www.pmpalliance.org/

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Discussion:
Best Practices in Opioid Therapy

- How are the social concerns of abuse and misuse balanced with the needs of patients who are in legitimate pain and would benefit from chronic opioid therapy?
- What are the best practices to achieve this balance?
  - Educational initiatives
    - Publications and other media
    - Mentoring
    - REMS
  - Medical education
    - Undergraduate
    - Postgraduate

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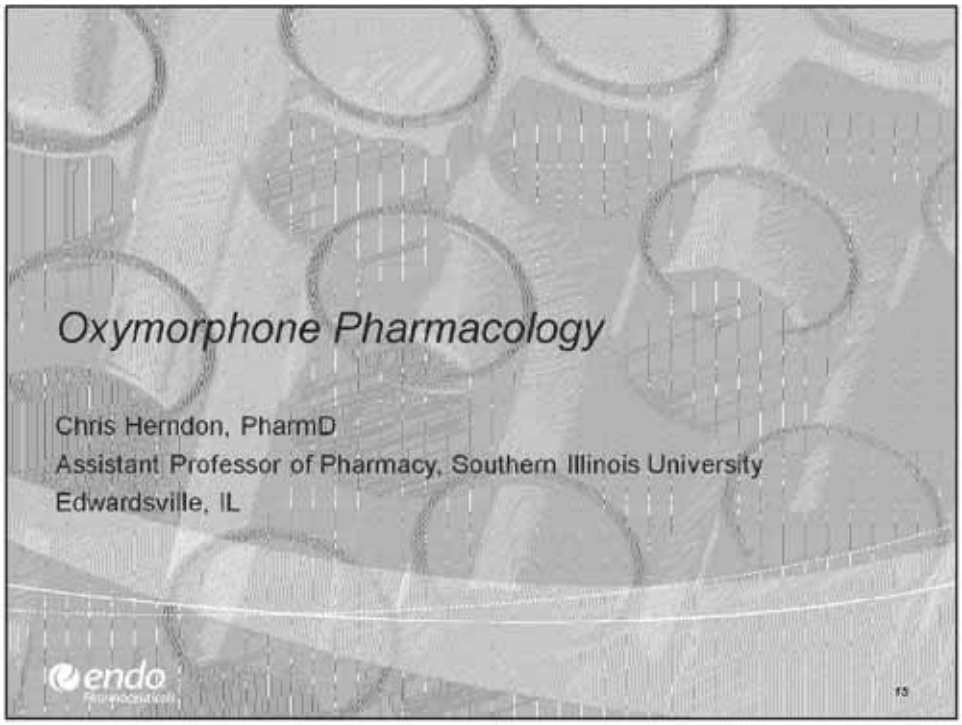
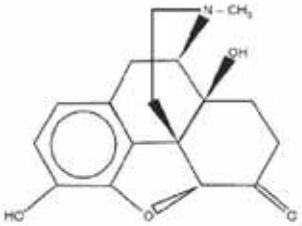


Oxymorphone Pharmacology
Chemistry – Receptor Affinity

- Pure semisynthetic opioid agonist relatively selective for the μ receptor[1] and less affinity for the δ,[1] δ,[2] and κ opioid receptor subtypes[2]
- Molecular structure similar to morphine but with greater lipid solubility[1]
- Ceiling to analgesic effects imposed only by AE[1]
- Patients aged >65 years require 40% lower dose vs patients aged 18–40 years[1]
- Half-life is often described as "long"
  - 1.3 hours with IV formulation[3]
  - 7.3 hours with IR formulation (5 mg)[4]
  - 11.3 hours with ER formulation (5 mg)[1]



1. OPANA® ER (oxymorphone hydrochloride extended-release tablets). Full PI, Endo Pharmaceuticals, 2012.
2. Metzger et al. J Med Chem. 2001;44(6):857-862.
3. Numorphan® (oxymorphone hydrochloride injection). Full PI, Endo Pharmaceuticals, 2012.
4. OPANA® IR (oxymorphone hydrochloride immediate-release tablets). Full PI, Endo Pharmaceuticals, 2010.

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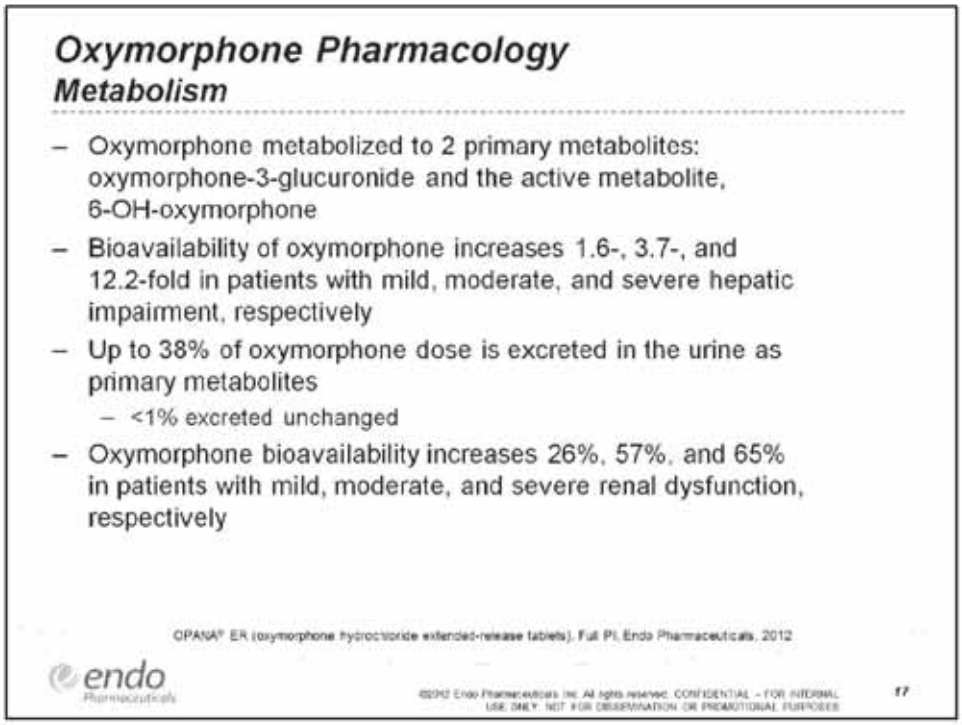


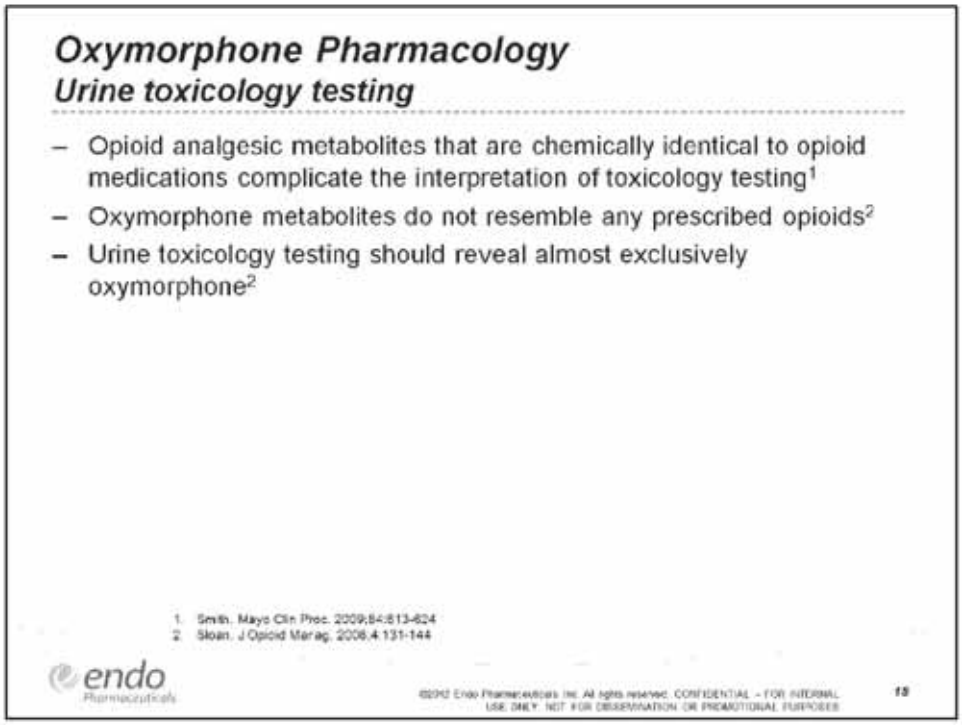
• Oxymorphone is highly metabolized, principally in the liver, and undergoes reduction or conjugation with glucuronic acid to form both a major active metabolite, 6-OH-oxymorphone, and inactive metabolite, oxymorphone-3-glucuronide.

• As a consequence of the important metabolic role of the liver in oxymorphone metabolism and clearance, the bioavailability of oxymorphone increases from 1.6-fold in patients with mild hepatic impairment to 3.7-fold in patients with moderate hepatic impairment, and to 12.2-fold in patients with severe hepatic impairment.

• Less than 1% of an oxymorphone dose is excreted in the urine unchanged. In subjects with normal hepatic and renal function, approximately 33%–38% of the dose is excreted as the primary glucuronide metabolite, oxymorphone-3-glucuronide.

• A pharmacokinetic study involving 24 patients with renal dysfunction found an increase of 26%, 57%, and 65% in oxymorphone bioavailability in patients with mild (creatinine clearance 51–80 mL/min), moderate (creatinine clearance 30–50 mL/min), and severe (creatinine clearance <30 mL/min) renal impairment, respectively, compared with healthy controls.

Reference: OPANA® ER (oxymorphone hydrochloride extended-release tablets). Full Prescribing Information, Endo Pharmaceuticals Inc., Chadds Ford, PA, 2012



- Opioid analgesics with metabolites that are chemically identical to other opioid medications can complicate the interpretation of toxicology testing.[1]
- Oxymorphone may offered an advantage in this regard because it is not metabolized into any available opioids or their metabolites.[2] As a consequence, urine toxicology testing for patients receiving oxymorphone should reveal almost exclusively oxymorphone.

References

1. Smith HS. Opioid metabolism. *Mayo Clin Proc.* 2009;84(7):613-624.
2. Sloan PA, Barkin RL. Oxymorphone and oxymorphone extended release: a pharmacotherapeutic review. *J Opioid Manag.* 2008;4(3):131-144.

• In vitro studies have shown that none of the major cytochrome P450 (CYP) isoenzymes (1A2, 2C9, 2C19, 2D6, 2E1, or 3A4) mediate the biotransformation of oxymorphone to 6-OH-oxymorphone at therapeutically relevant plasma concentrations.

• Likewise, oxymorphone incubated with human liver microsomes at a concentration of ≤50 µM was not shown to inhibit the major CYP isoenzymes.

• In healthy volunteers, neither low-dose oxymorphone extended release (20 mg every 12 hours orally) nor high-dose oxymorphone extended release (60 mg every 12 hours orally + naltrexone 50 mg once daily) induced or inhibited CYP3A4 or CYP2C9 enzyme activity.

• Thus, it is not expected that oxymorphone, or its metabolites, will act as inhibitors of any of the major CYP enzymes.

Oxymorphone Pharmacology
Dose Ceiling

- For all opioids, therapy with doses ≥180 mg/d morphine equivalents is controversial because of limited evidence of safety and efficacy and epidemiologic data associating high opioid doses with AEs (eg, falls in the elderly) and deaths from overdose[1,2]
- Limited data available for oxymorphone suggest that higher doses do not appear to be associated with a marked worsening of tolerability[3]
  - A post hoc analysis of pooled data from 422 patients with chronic pain from 10 clinical trials of oxymorphone ER ≥60 mg/d (equivalent to ≥180 mg/d morphine) was conducted to describe the AE profile of high-dose oxymorphone ER
  - With increasing dose, the frequency of AEs typically associated with opioids showed small increases (<10%), no change, or small decreases
  - Some AEs not commonly associated with opioids (ie, anxiety, pyrexia, upper respiratory infections) were reported at least 3-fold more frequently with the higher doses of oxymorphone ER relative to the lower doses

1. Saunders et al. J Gen Intern Med. 2010;25:310-315
2. Gomes et al. Arch Intern Med. 2011;171:686-691
3. Gould & Wieman. Consult Pharm. 2012;27(10):698-716

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Oxymorphone Pharmacology
Euphoria and Cognitive/Psychomotor Effects

- A study in healthy volunteer recreational opioid users found single intact doses of oxymorphone ER produce less positive subjective effects (eg, euphoria) and less cognitive/psychomotor impairment compared with single intact equianalgesic doses of oxycodone controlled release (CR)[1,2]
- Intensity of positive subjective effects is one of several factors making a drug attractive for abuse[3]
- Psychomotor impairment can lead to falls in the elderly[4]
- The methodology of this study could not distinguish the extent to which the molecule or the formulation contributed to the observed differences
  - The pharmacokinetics of drug release differed substantially between oxymorphone ER and oxycodone CR[1,2]
  - Crushing of oxycodone CR tablets can have a radical effect on subjective effects and has not been studied with oxymorphone ER[5]

1. Schoedel et al. Pain Physician. 2010;13:561-573.
2. Schoedel et al. J Opioid Manag. 2011;7:179-192.
3. Butler et al. Harm Reduct J. 2006;3:5-16.
4. Saunders et al. J Gen Intern Med 2010;25:310-315.
5. Webster et al. Pain Medicine 2012;13:790-801.

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Discussion:
Oxymorphone Pharmacology

- Are there aspects of oxymorphone pharmacology of which prescribers need to be more aware?
  - Metabolism
  - Interpretation of urine toxicology
  - Drug-drug interactions/combination therapy
  - Dose ceiling/high-dose therapy
  - Euphoria and cognition
- Are there aspects of oxymorphone pharmacology requiring further research?
- Suggestions for educational activities?

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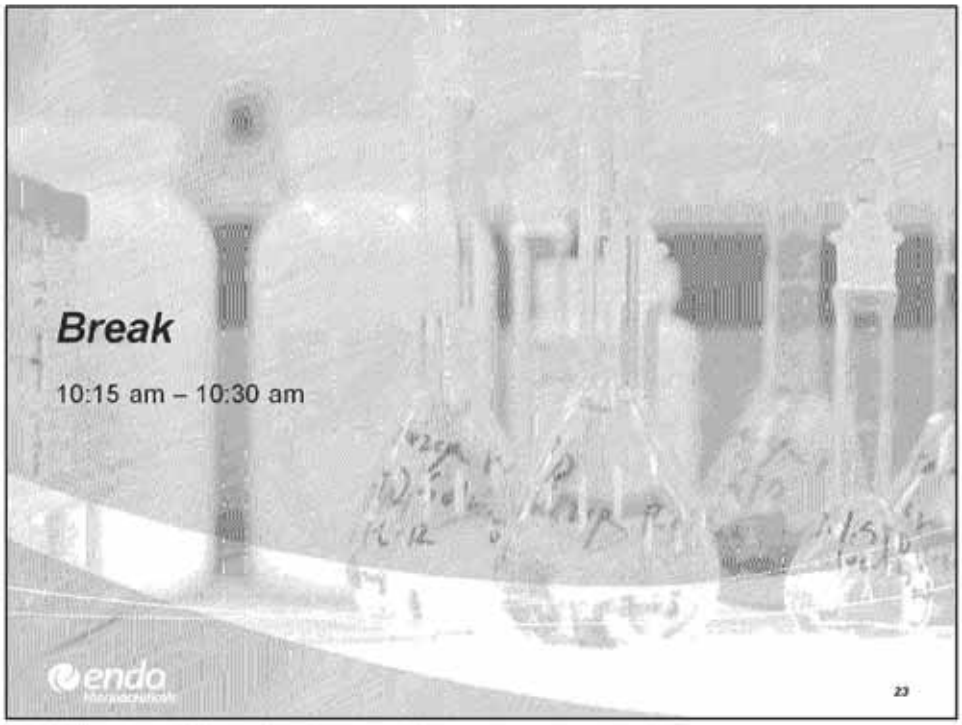
Break
10:15 am – 10:30 am
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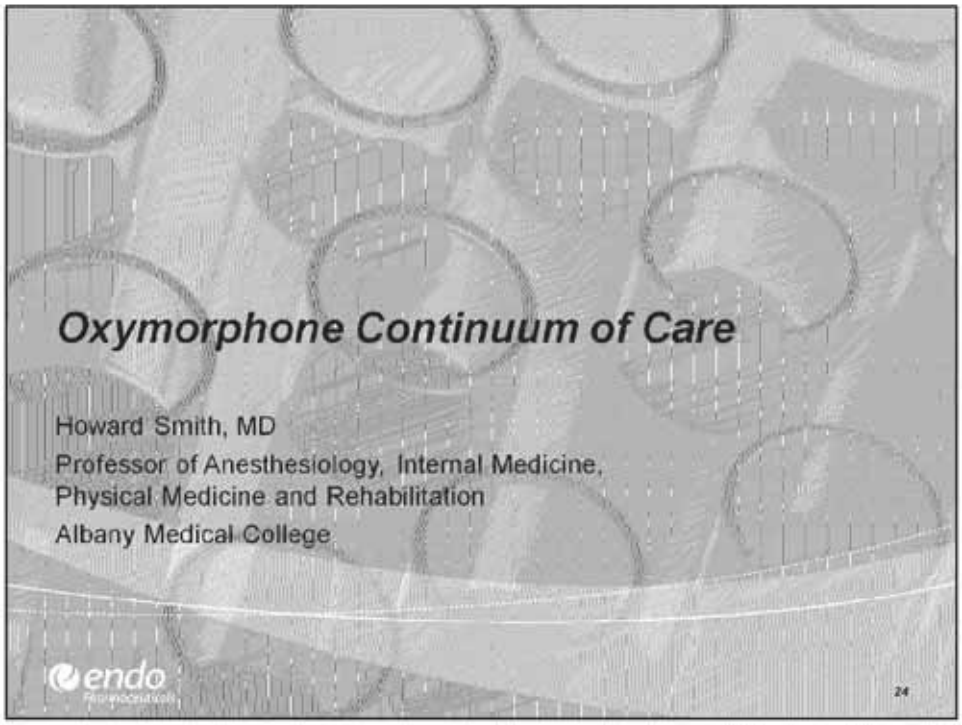
Oxymorphone Continuum of Care
Howard Smith, MD
Professor of Anesthesiology, Internal Medicine, Physical Medicine and Rehabilitation
Albany Medical College
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Oxymorphone Continuum of Care

- Available formulations
  - Oxymorphone ER
  - Oxymorphone IR
  - Oxymorphone injection
- Other formulations – value?
  - Oral liquid - ?
  - Suppository - ?
  - Transdermal - ?
  - Fixed-dose combinations?

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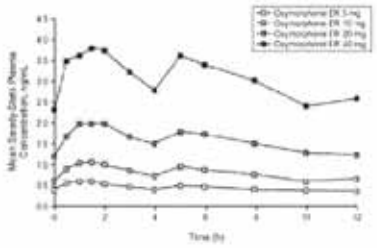
Oxymorphone Continuum of Care
Oxymorphone ER

- Bioavailability ~10% after oral administration[1]
- OPANA® ER exhibits linear, dose-proportional pharmacokinetics at doses ranging from 5–40 mg[2]
- Steady state achieved in 3 days
- C_{max} is 2.5–4.0 hours (single dose)
- Plasma levels increased following fatty meals
- $t_{1/2}$ 11.3 hours for 5-mg dose[1]

Mean steady-state plasma concentrations after multiple-dose administration of 5, 10, 20, and 40 mg



1. OPANA® ER (oxymorphone hydrochloride extended-release tablets). Full PI, Endo Pharmaceuticals, 2012
2. Adams & Ahdieh. Pharmacotherapy. 2004;24:468-476

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Oxymorphone Continuum of Care
Reformulated Oxymorphone ER

- On December 9, 2011, the FDA approved oxymorphone ER reformulated with a hardened polyethylene oxide (PEO) matrix (INTAC™, Grünenthal GmbH, Aachen, Germany) designed to be crush resistant
  - Oxymorphone ER with the PEO matrix replaced the previous formulation of oxymorphone ER, which had a polysaccharide hydrogel (PSH) matrix (TimeRx®; Endo Pharmaceuticals Inc., Chadds Ford, PA) in February 2012
- 3 open-label, randomized, single-dose crossover studies were completed to demonstrate bioequivalence of oxymorphone ER-PEO and oxymorphone ER-PSH[1]
  - EN3288-103: 40-mg tablets in fasted subjects
  - EN3288-104: 40-mg tablets in fed subjects
  - EN3288-105: 5-mg tablets in fasted subjects
  - The 3 studies shared a similar methodology
- Bioequivalence of oxymorphone ER-PEO and oxymorphone ER-PSH was demonstrated in fasted and fed subjects taking 40-mg tablets and in fasted subjects taking 5-mg tablets[1]

1. Benedek et al. Drug Des Devel Ther. 2011;5:455-463.

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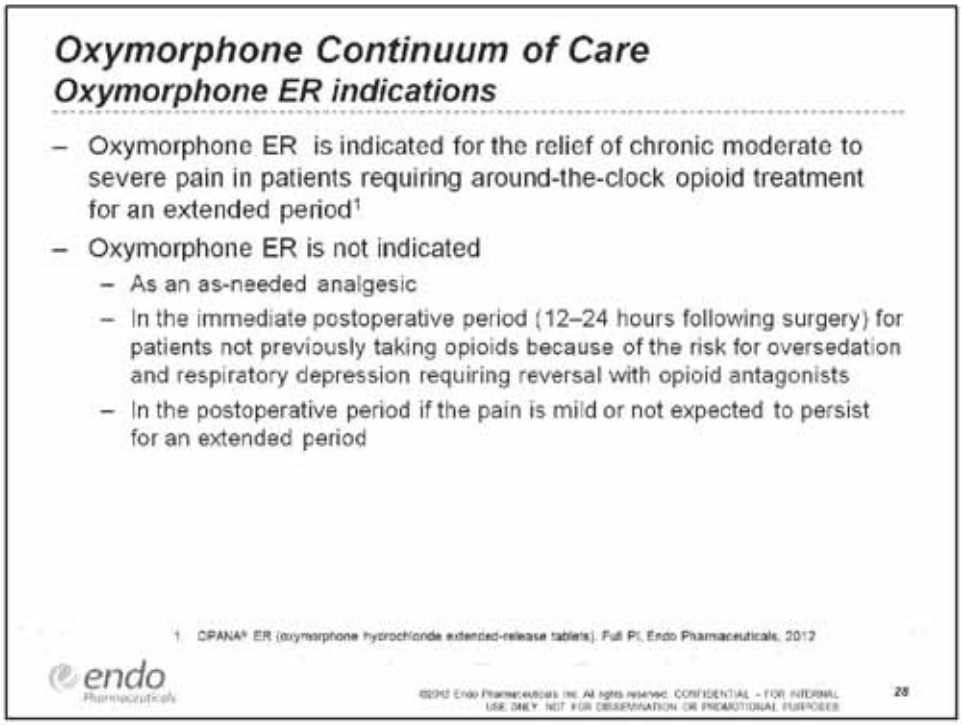
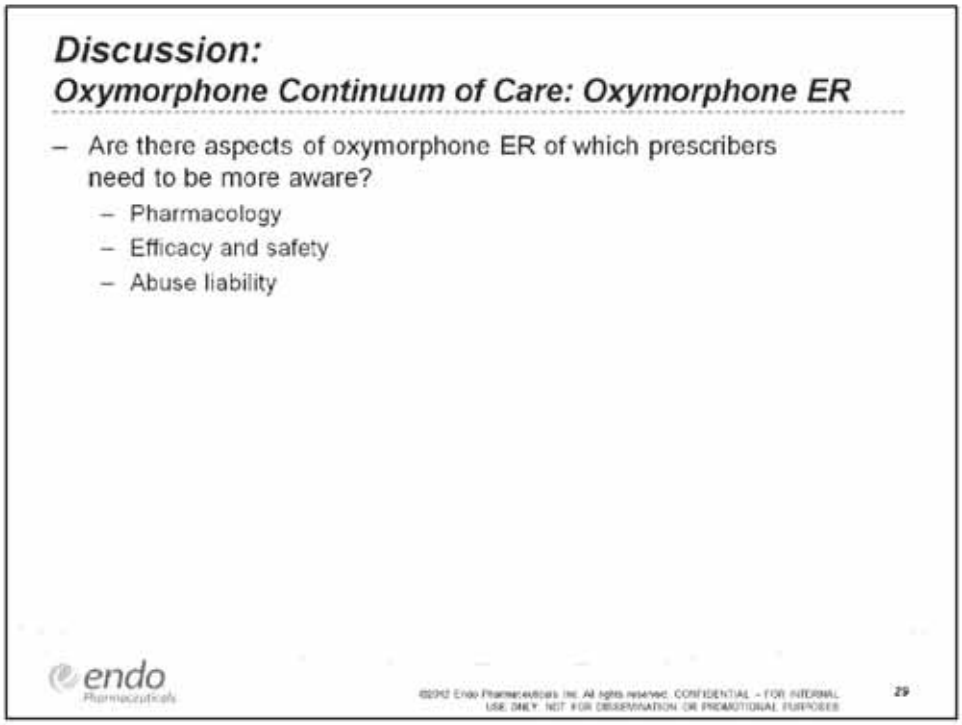


• Oxymorphone ER is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

• Oxymorphone ER is not indicated as an as-needed analgesic, or in the immediate postoperative period (12–24 hours following surgery) for patients not previously taking opioids, because of the risk for oversedation and respiratory depression requiring reversal with opioid antagonists. In addition, oxymorphone ER is not indicated in the postoperative period if the pain is mild or not expected to persist for an extended period of time.



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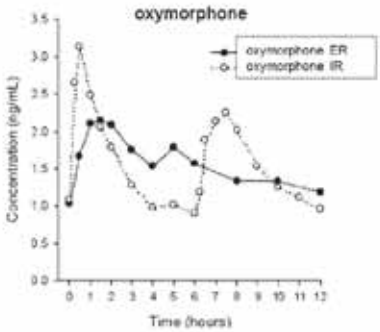
Oxymorphone Continuum of Care
Oxymorphone IR

- The single-dose profile following oral administration of oxymorphone IR is characterized by a short time to peak concentration (t_{max}), a rapid distribution phase, and ≥1 slower elimination phase
- The median t_{max} following oral administration was 0.5 hours and $t_{1/2}$ was 7.3 hours (5-mg dose)
- The plasma concentrations following administration of the IR tablet are subject to peak-to-trough swing and are increased after fatty meals



INVESTIGATIONAL DRUG BROCHURE. PROJECT EN3202/EN3203 – Oxymorphone ER/IR. DOCUMENT EDITION DATE: February 27, 2003

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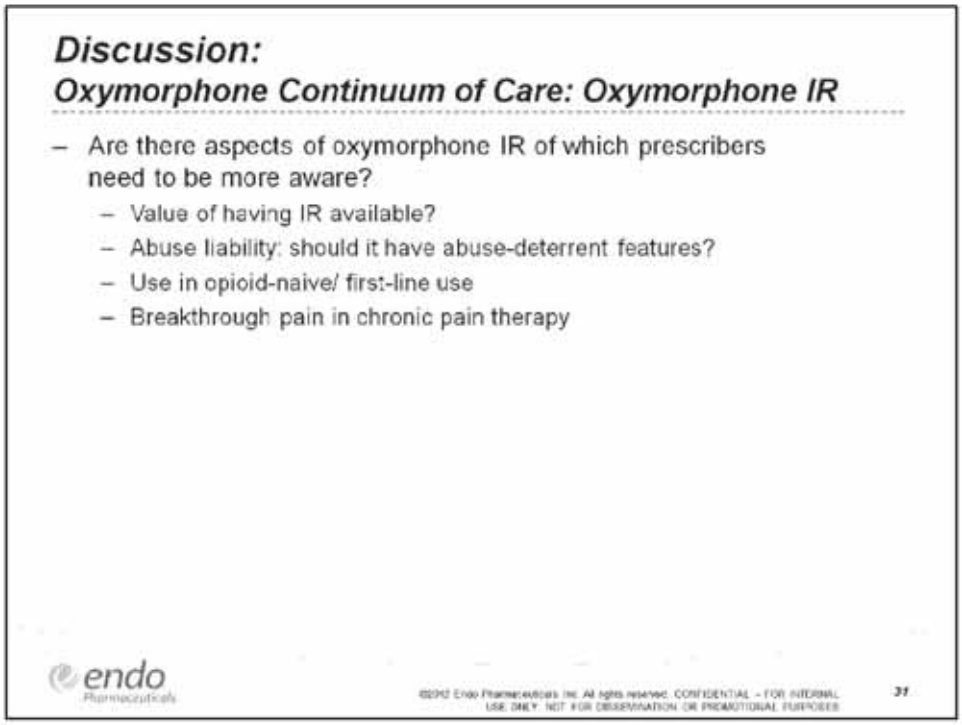
Discussion:
Oxymorphone Continuum of Care: Oxymorphone IR
– Are there aspects of oxymorphone IR of which prescribers need to be more aware?
– Value of having IR available?
– Abuse liability: should it have abuse-deterrent features?
– Use in opioid-naive/ first-line use
– Breakthrough pain in chronic pain therapy
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Discussion:
Oxymorphone Continuum of Care: Oxymorphone Injection

- How is oxymorphone injection used and why?
  - Limited literature: better relief, less sedation vs morphine[1]
  - Patient type
    - Complicated patients
    - Labor and delivery
    - Multiple allergies/opioid intolerance
    - Polypharmacy/drug interactions
    - Intractable pain
    - Acute postoperative pain refractory to other opioids
  - Care setting
    - OR
    - Emergency
    - ICU
    - Interventions/procedures
    - PCA

1. Sinatra et al. Anesthesiology. 1989;71:502-507

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Discussion:

Oxymorphone Continuum of Care: Oxymorphone oral liquid

- How would you use an oral liquid formulation?
  - Patient type
    - Geriatrics/pediatrics
    - Psychiatric
    - ENT
    - Cancer
    - Patient preference
  - Care setting

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Lunch
12:00 pm – 12:45 pm
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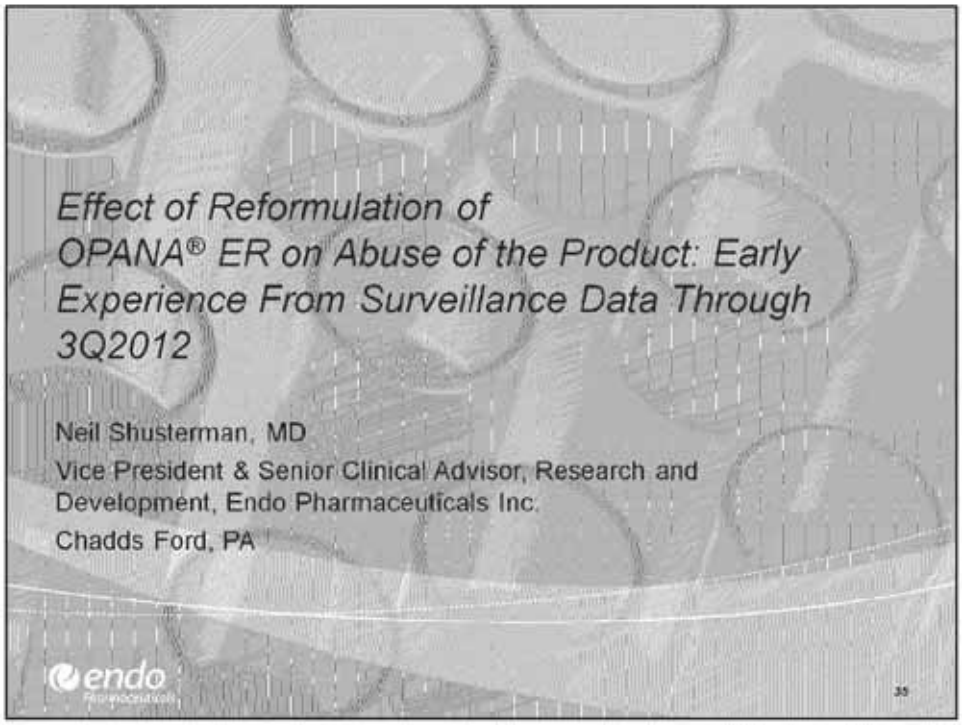

Content

- The rationale for reformulation of OPANA® ER
- Early results of the effect of the reformulation
  - How is the effect being measured?
  - What does the data show?

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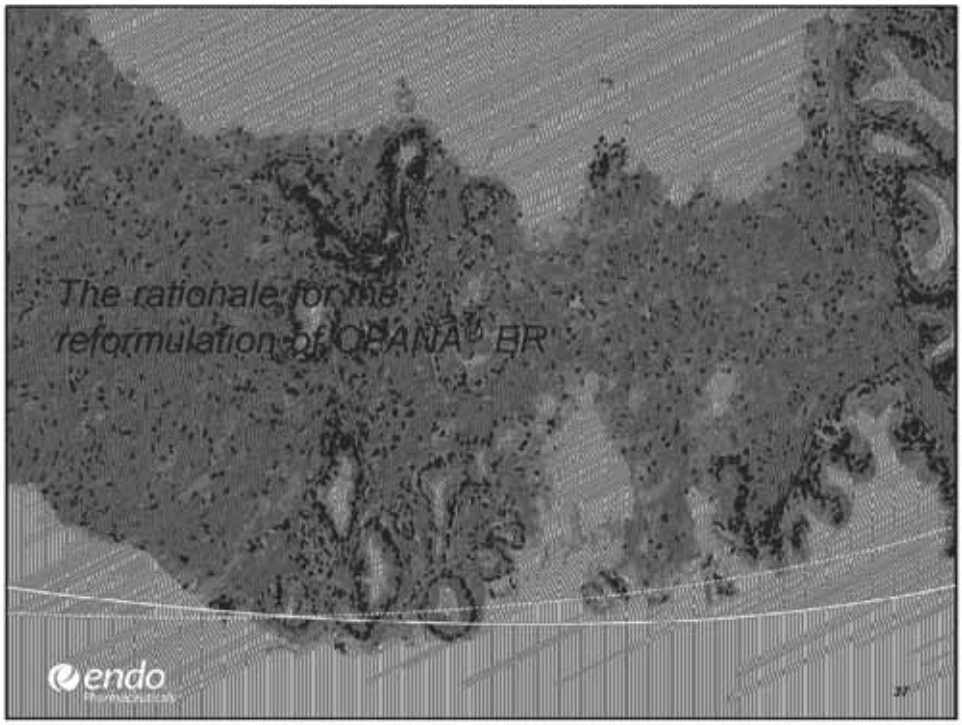
The rationale for the reformulation of OPANA® ER
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The Opioid Problem

Rates of Prescription Painkiller Sales, Deaths and Substance Abuse Treatment Admissions (1999–2010)

Sources: National Vital Statistics System, 1999-2008; Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA), 1999-2010; Treatment Episode Data Set, 1999-2009.

CDC: http://www.cdc.gov/vitalsigns/painkilleroverdoses/

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Prescription Drug Abuse

- Since market introduction of OPANA® ER in 2006, Endo has been involved in many efforts to control abuse, misuse, and diversion
  - Monitoring efforts have shown that the majority of abuse is through the nasal route, where individuals insufflate (inhale through the nose) the drug
- Endo directed research efforts to finding a tablet that would resist efforts to crush it
  - While allowing the active medication to be absorbed after being swallowed by patients needing appropriate pain relief
- The US FDA approved the crush-resistant formulation (CRF) of OPANA® ER on December 9, 2011
  - Commercial introduction of this formulation in February 2012

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Design Considerations for the New Formulation

- Impact the major route of abuse of OPANA® ER
  - Crushing and subsequent insufflation
- Manufactured to be at least 5–10 times harder than the original tablet

Object	Hardness (N)
OPANA® ER CRF	>1000
Typical tablet	<200
OPANA® ER	71–125
Hammer strike	~5000
Maximum single human bite	~550

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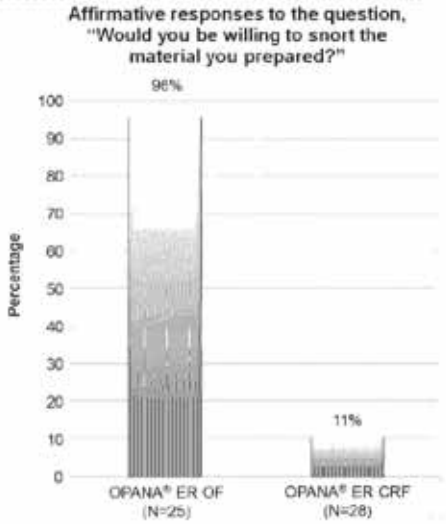
Premarket Research – Crushing and Snorting

- Individuals skilled in the crushing and snorting of opioid drugs were allowed to tamper with original OPANA® ER tablets and OPANA® ER CRF tablets
- Instructed to prepare each tablet as if they were going to snort it



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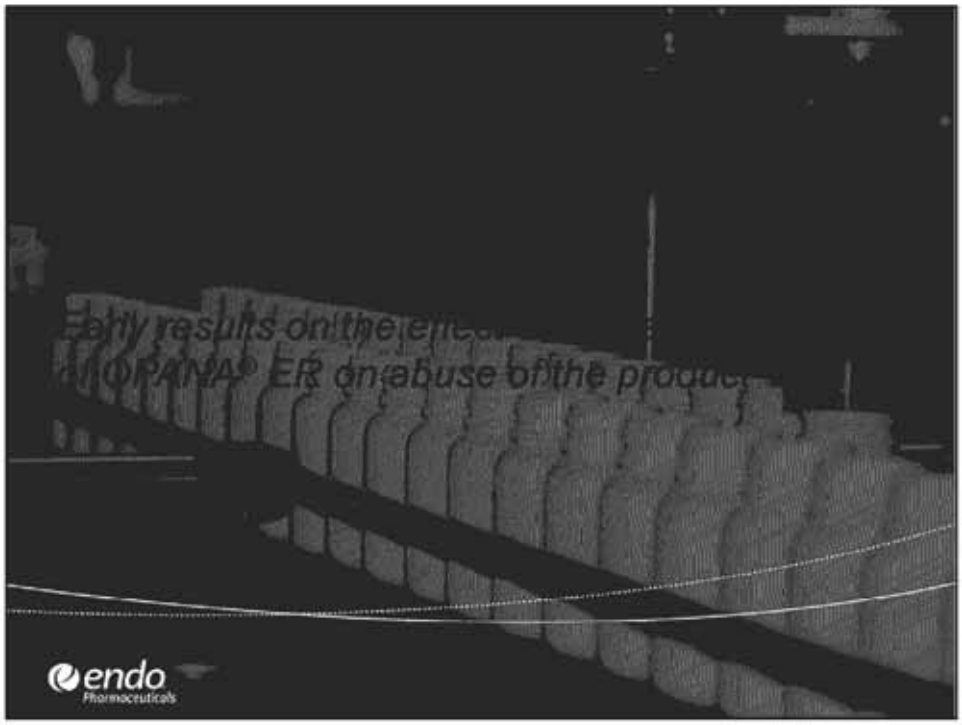
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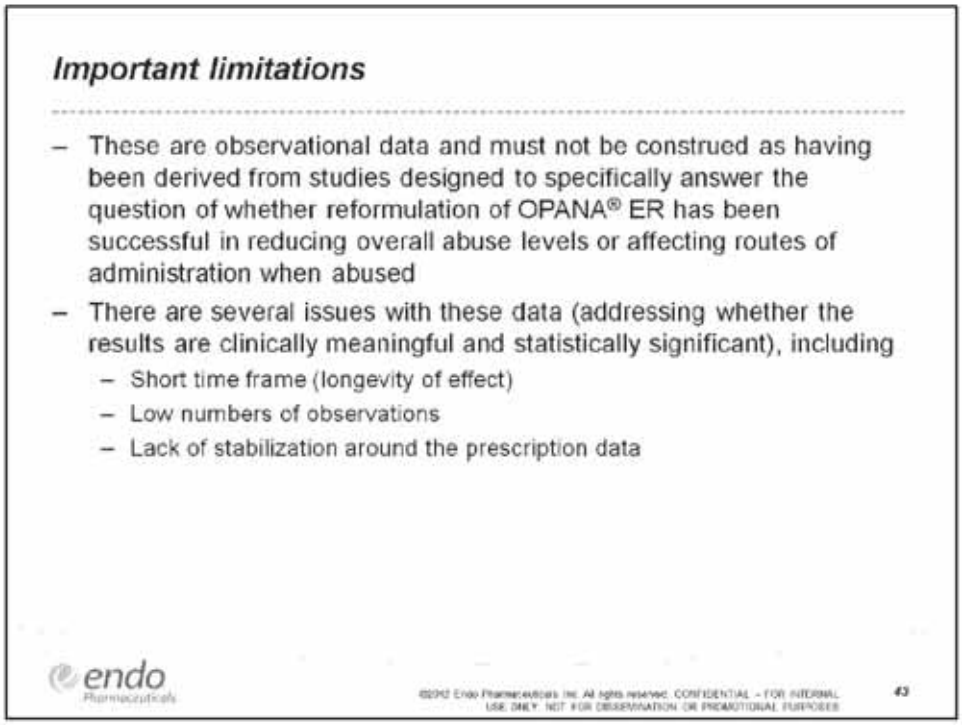
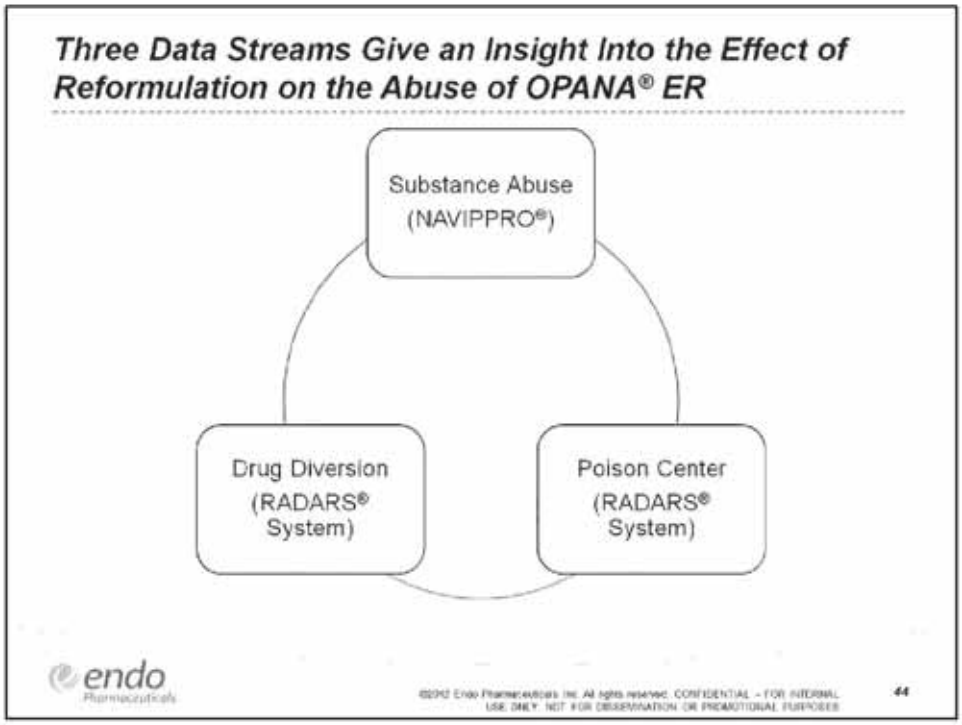
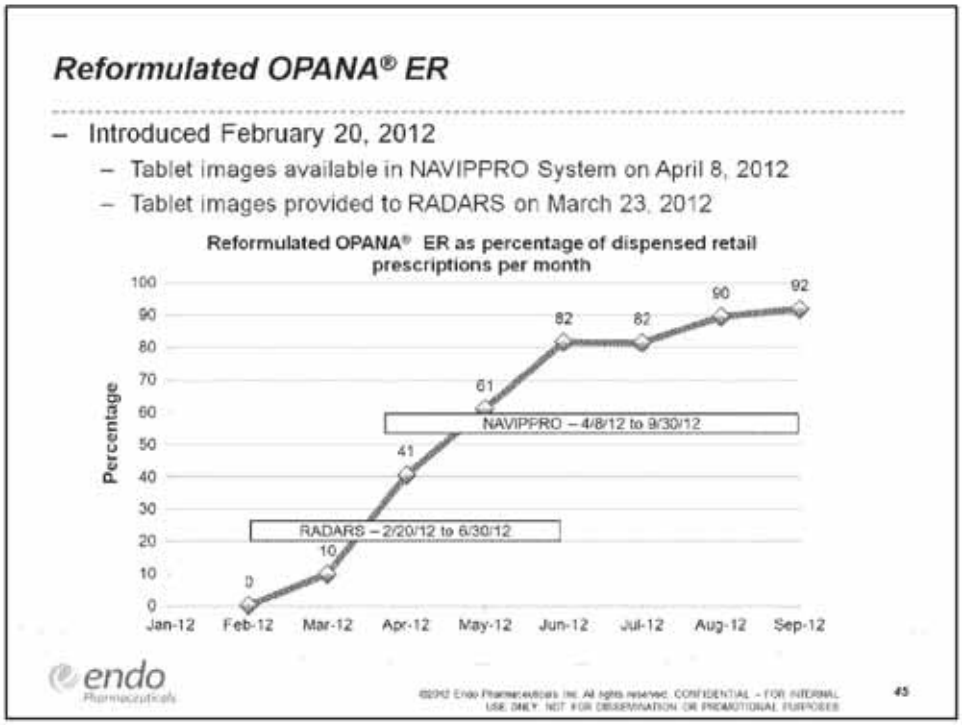


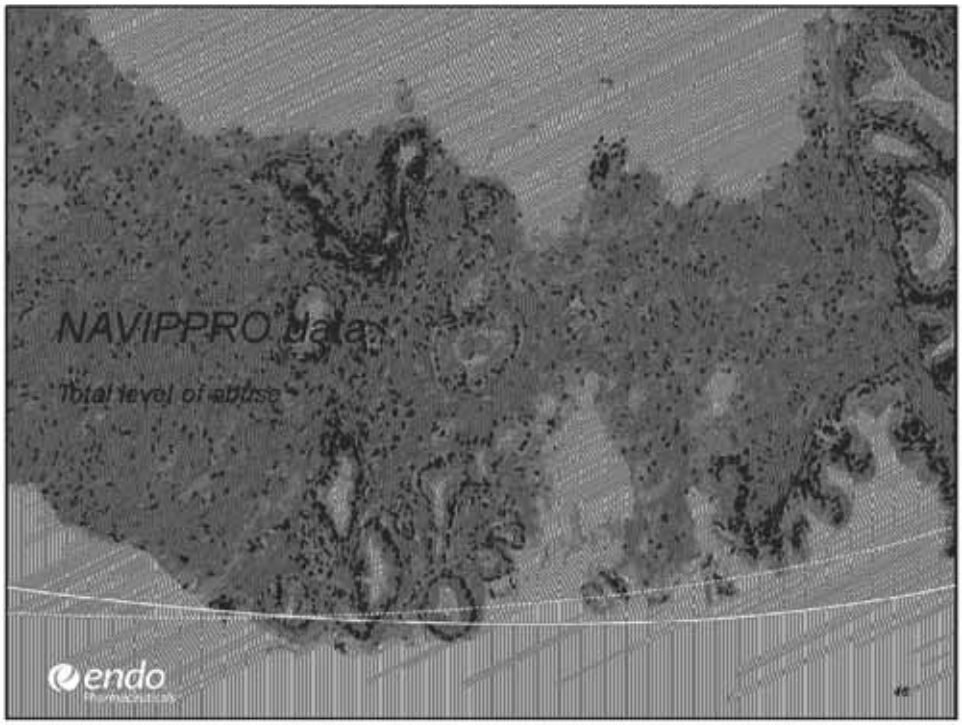
Limitations



Three streams of data about abuse come from 2 sources (NAVIPPRO and RADARS)



Graph represents uptake of reformulated Opana ER during 2012 after introduction in February. Horizontal bars represent time periods for each data stream that covers new formulation. Feb 20, 2012 was first date new formulation shipped to retail pharmacies.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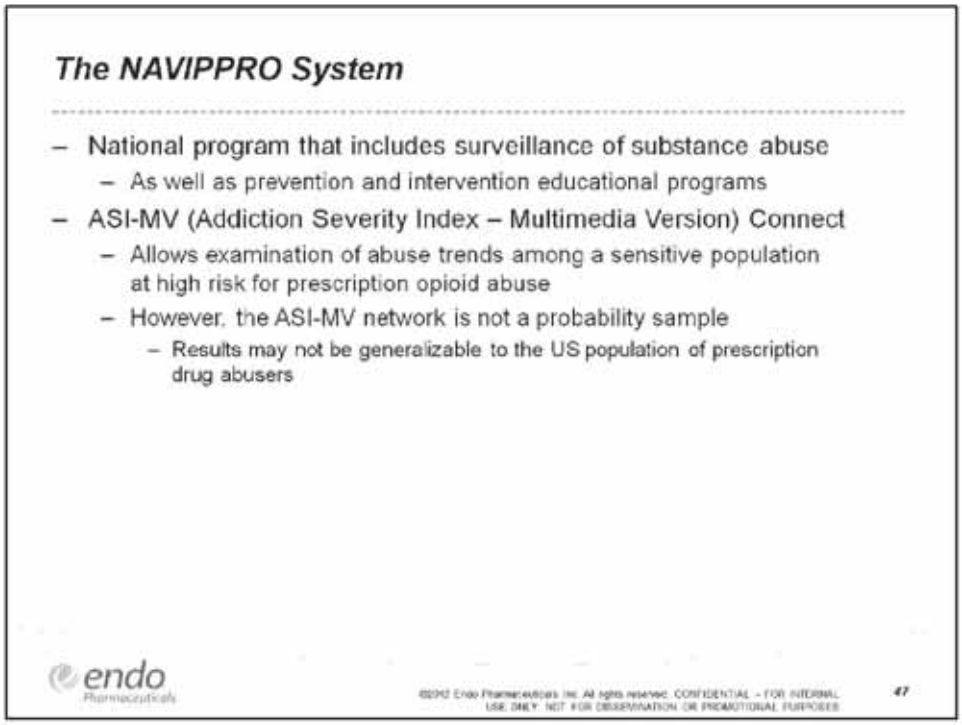
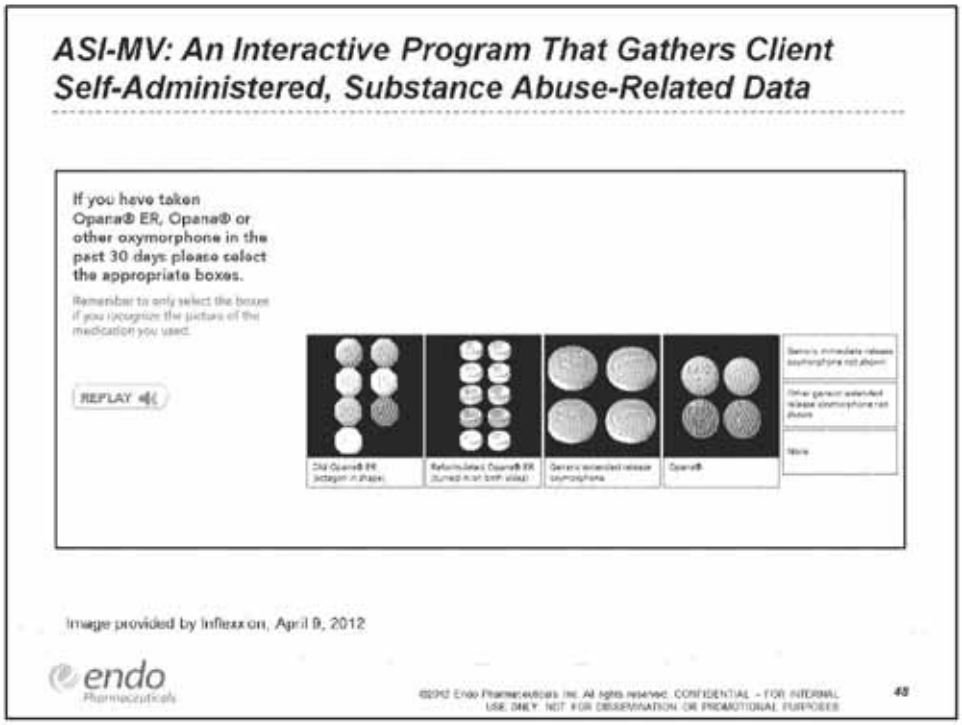
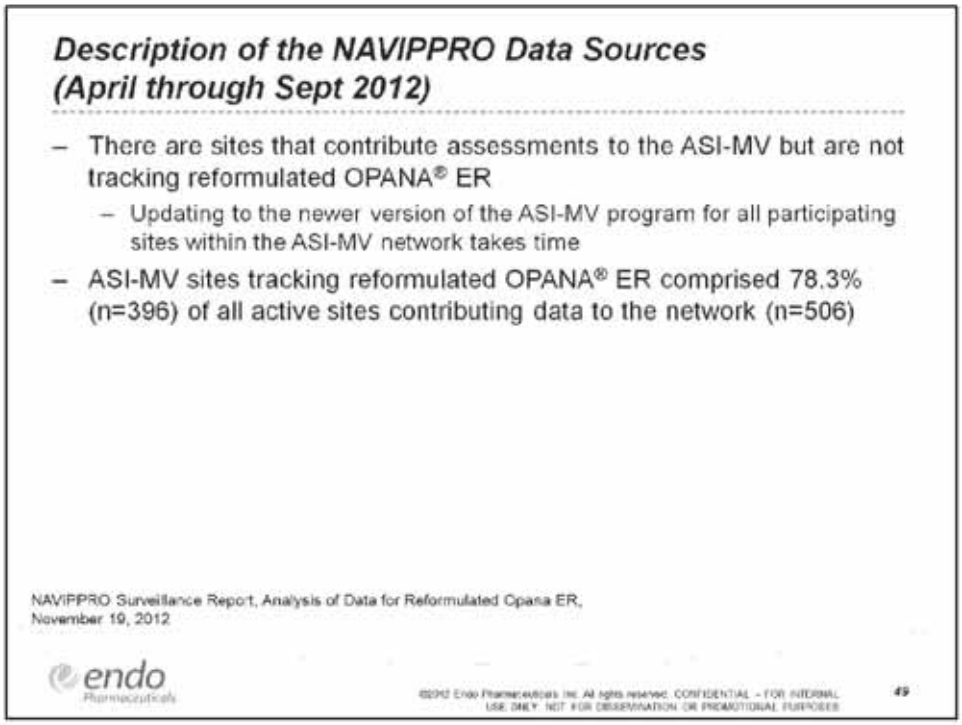


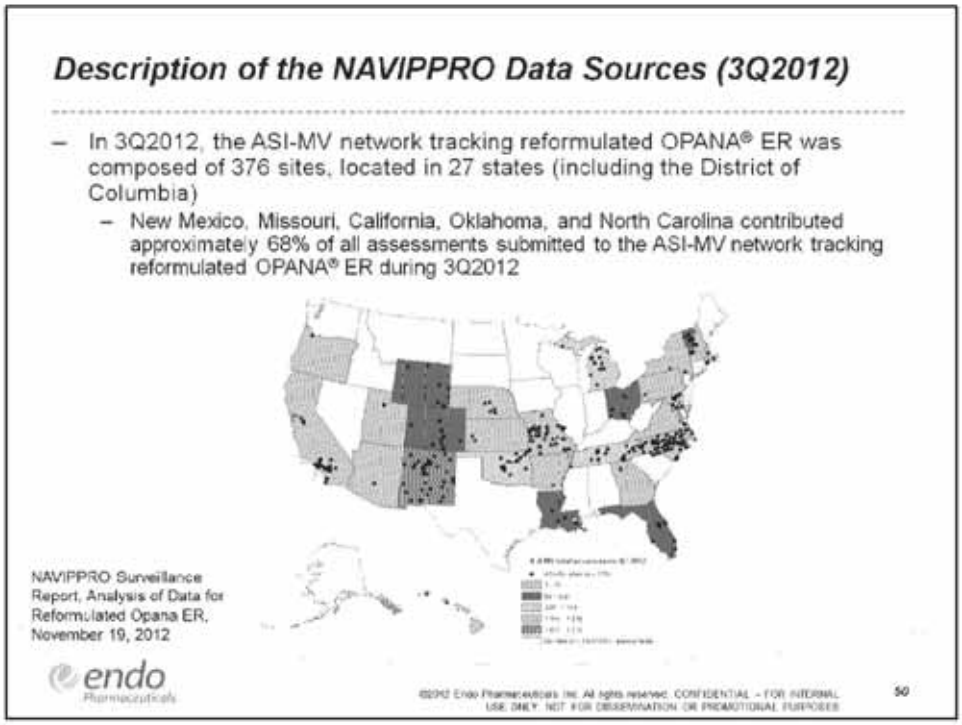
Explanation of NAVIPPRO System and ASI-MV



Explanation of NAVIPPRO System and ASI-MV



Limitations of NAVIPPRO data sources during this period



National coverage of NAVIPPRO System. A "limitation" slide.

The NAVIPPRO Data Set

ASI-MV Participant Characteristics per Period

	2011	1Q2012	2Q2012	3Q2012
All respondents	70,744	18,108	11,095	14,371
Respondents reporting any past 30-day Rx opioid abuse	14,437	3610	2222	2988

Total Dispensed Prescriptions per Time Period*

	2011	1Q2012	2Q2012	3Q2012
OPANA® ER OF	1,069,867	238,103	54,129	14,652
OPANA® ER CRF	--	--	102,960	126,700
Generic oxymorphone ER	N/A	6334	9670	15,094

* Prescription data are derived from IMS Health, and only include prescriptions dispensed in states that contributed data to the ASI-MV network during the current reporting period.

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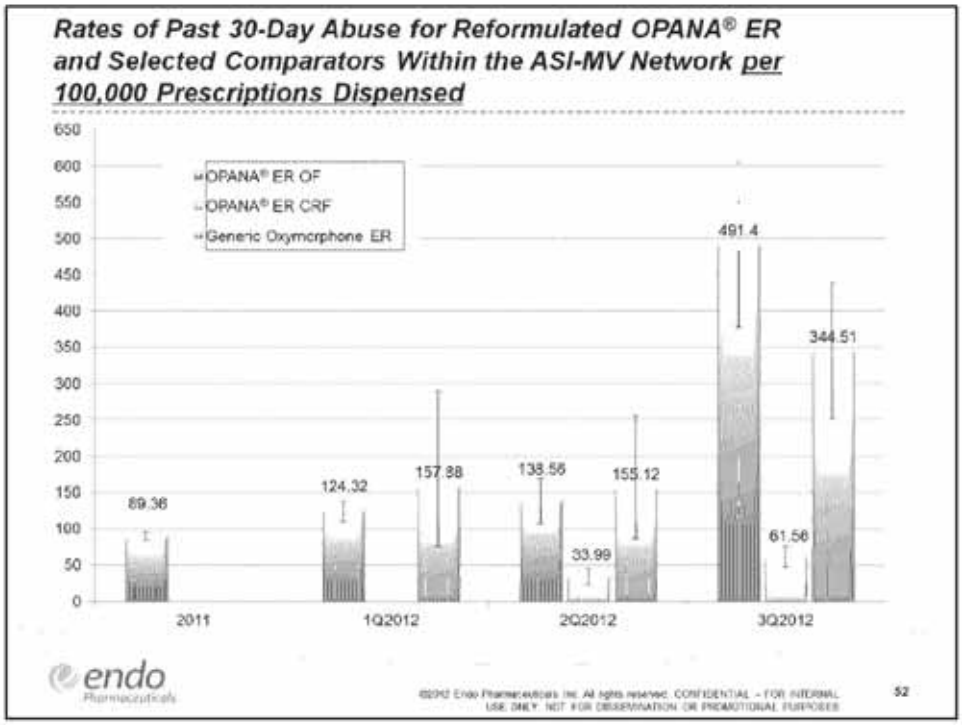
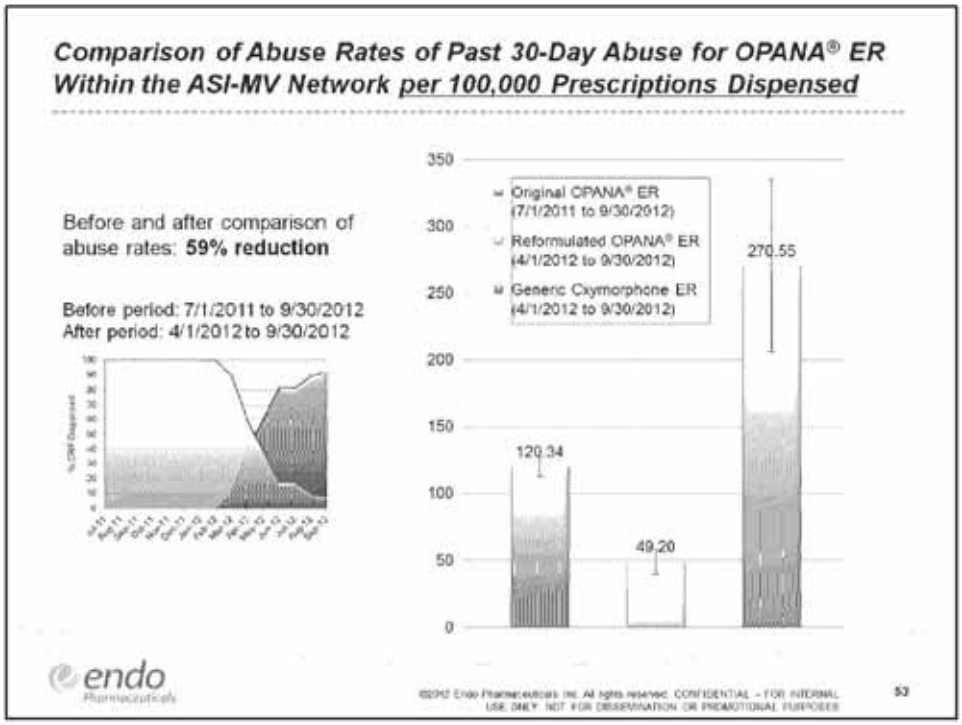
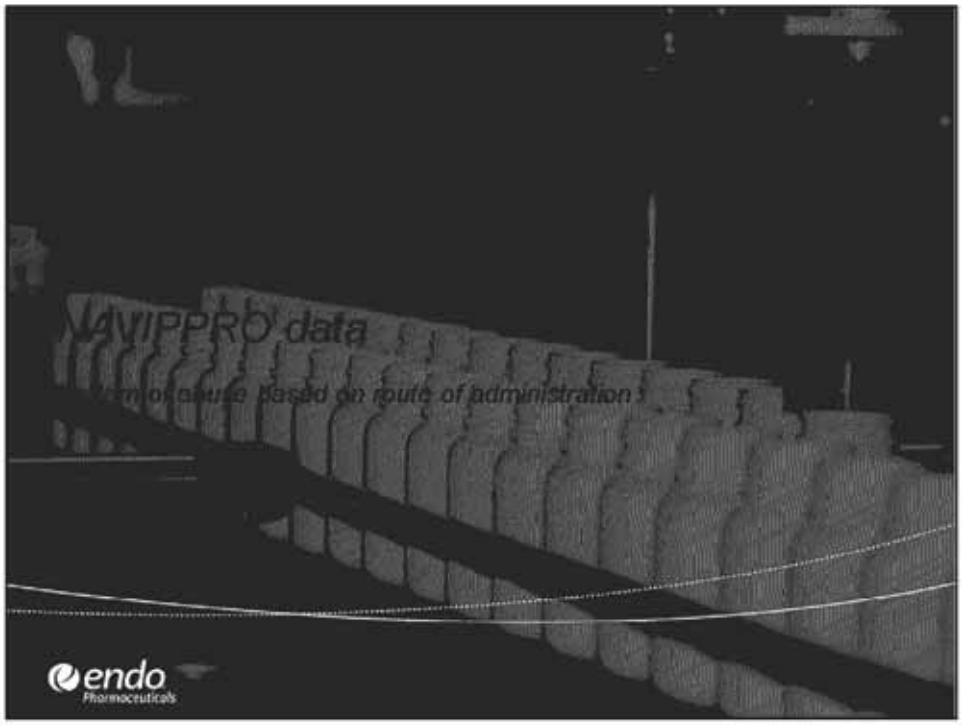


NAVIPPRO data by calendar quarter. **Notice inclusion of generic oxymorphone ER data.** This represents 2 low dose strengths that are on the market.



NAVIPPRO data using a "before" and "after" analysis. The "before" time started on 7/1/2011 and extended to data cutoff on 9/30/2012 and represents tracking of old Opana ER. The "after" time started on 4/1/2012 when NAVIPPRO started making the new tablet images available to their clients. Because both formulations were circulating after that point, notice the "overlap" of "before" and "after"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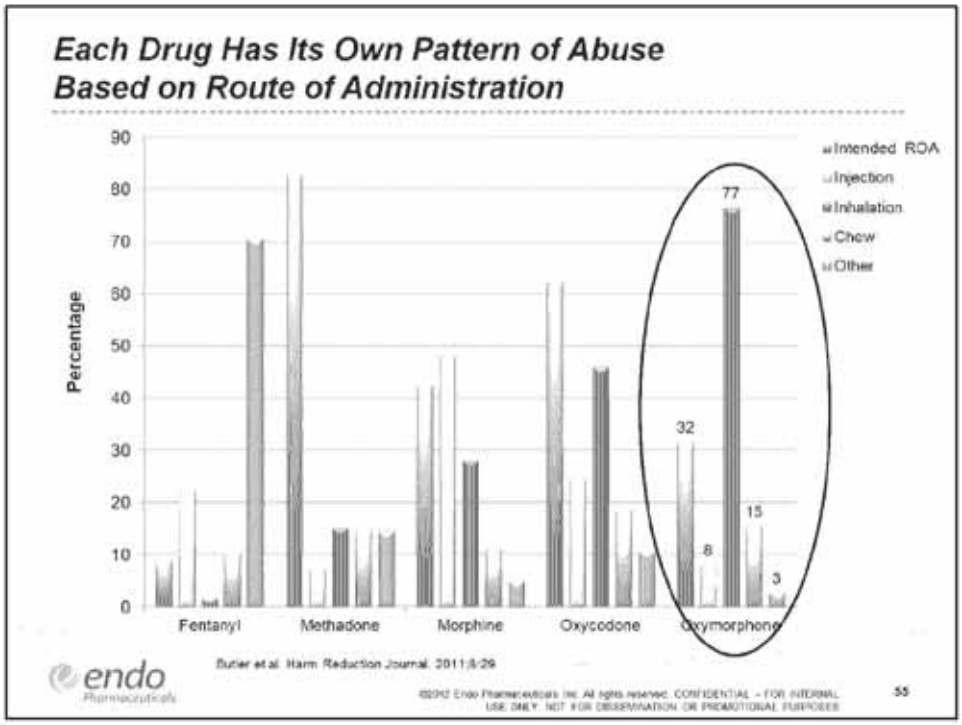
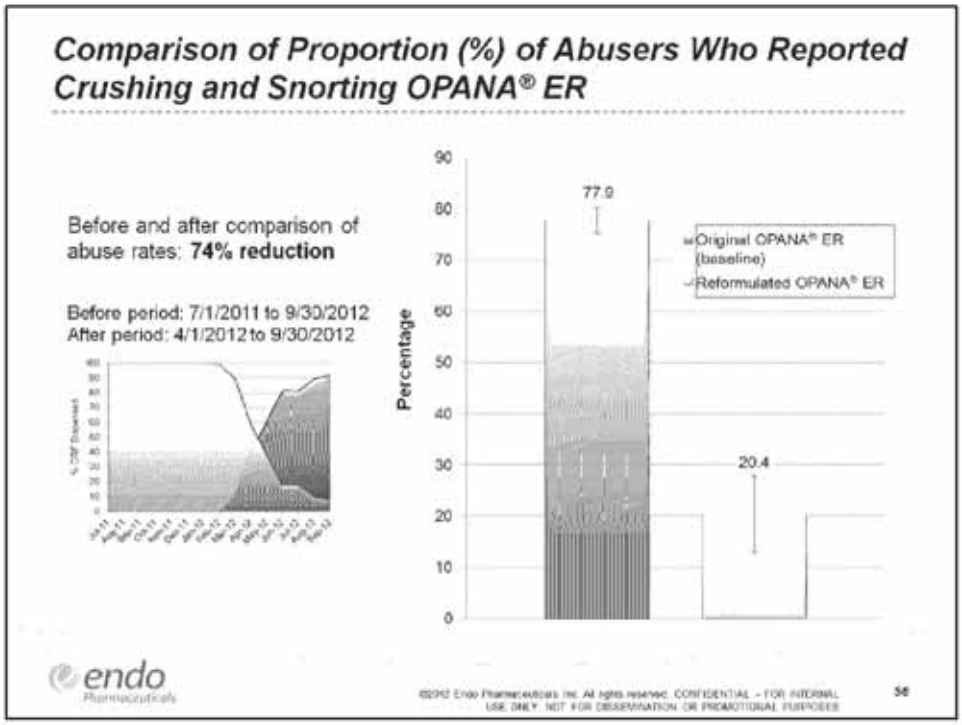
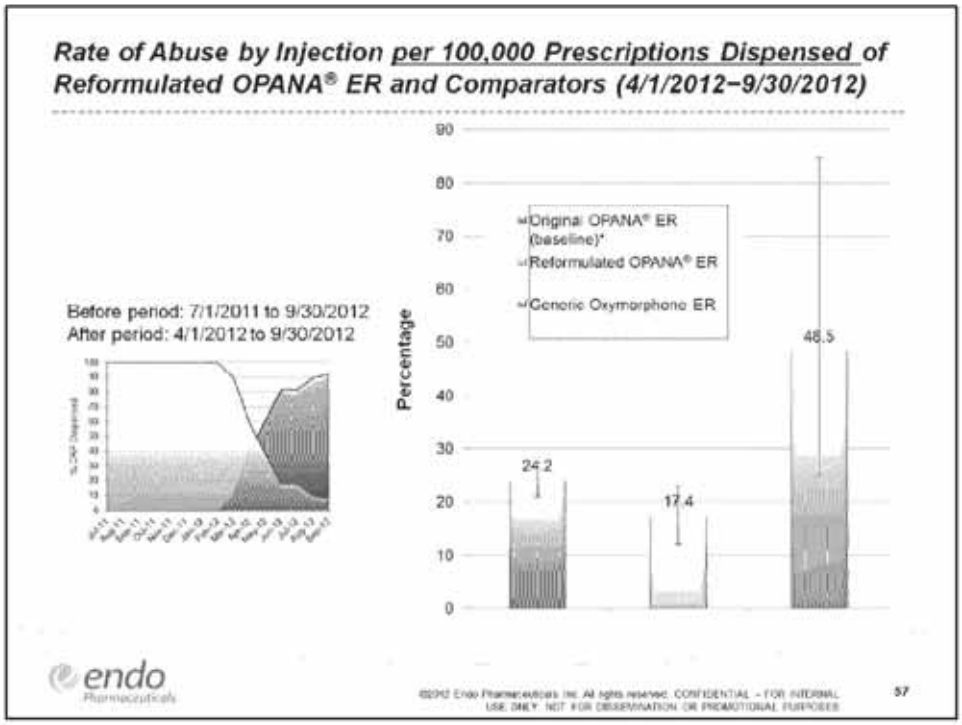


The historic pattern of abuse of each major opioid. Original Opana ER was heavily dominated by snorting.



A "before" and "after" comparison of snorting.


Rate of Abuse by Injection per 100,000 Prescriptions Dispensed of Reformulated OPANA® ER and Comparators (4/1/2012–9/30/2012)
Before period: 7/1/2011 to 9/30/2012
After period: 4/1/2012 to 9/30/2012
Percentage
90
80
70
60
50
40
30
20
10
0
Original OPANA® ER (baseline)*
Reformulated OPANA® ER
Generic Oxymorphone ER
24.2
17.4
48.5
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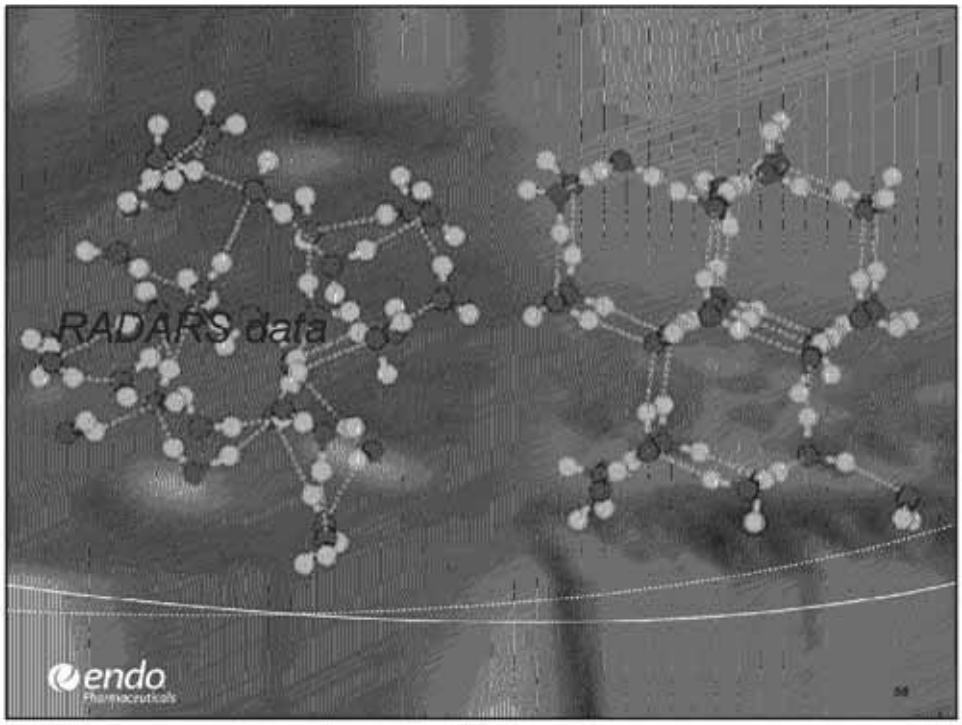
RADARS data
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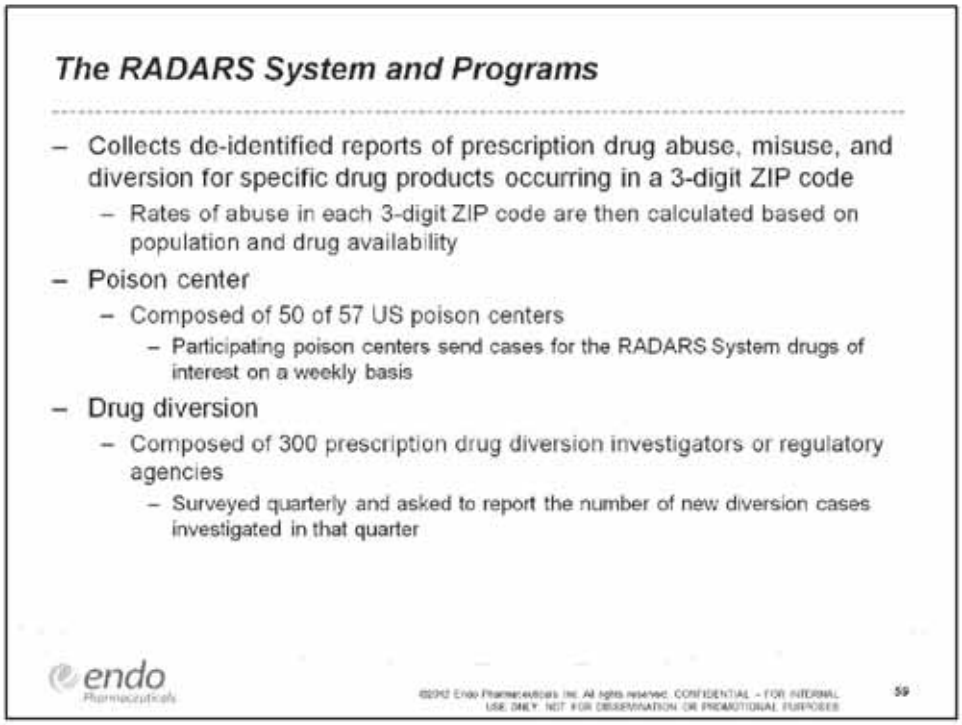
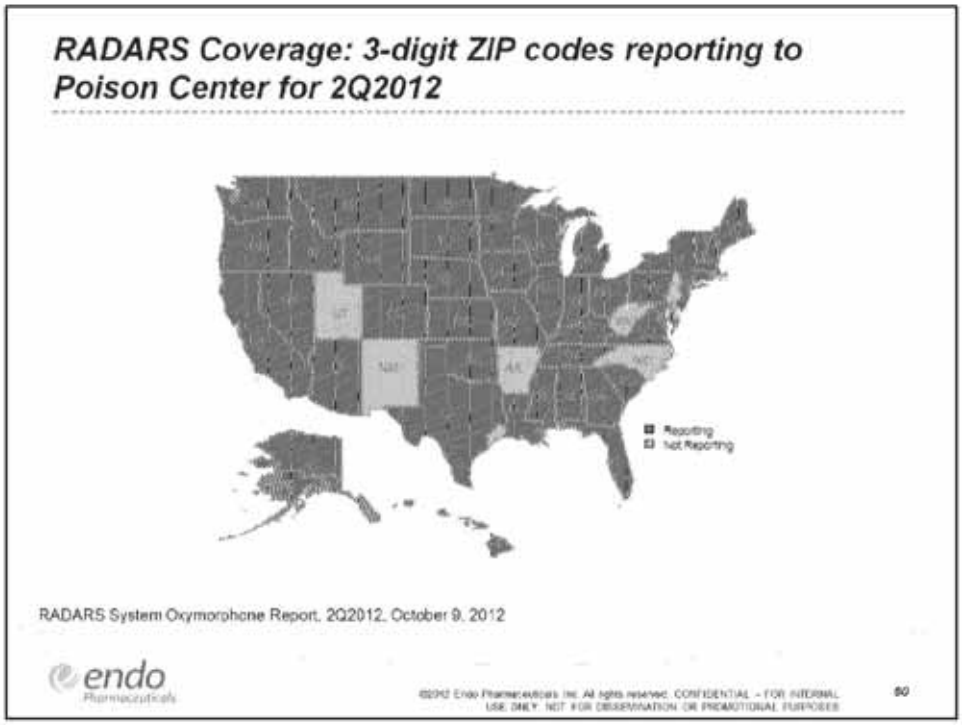
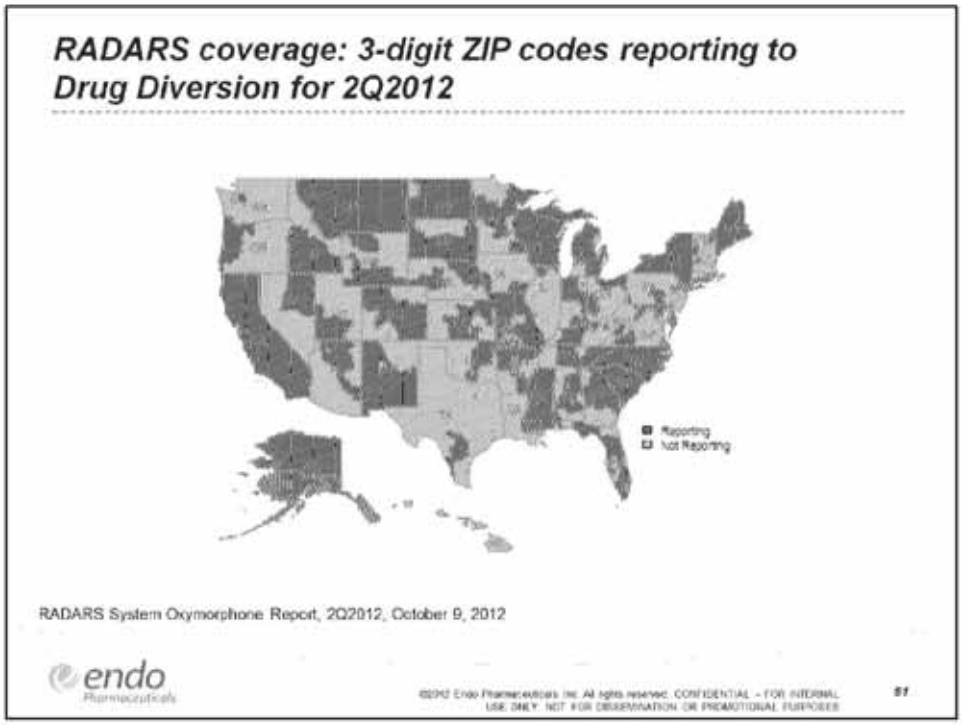


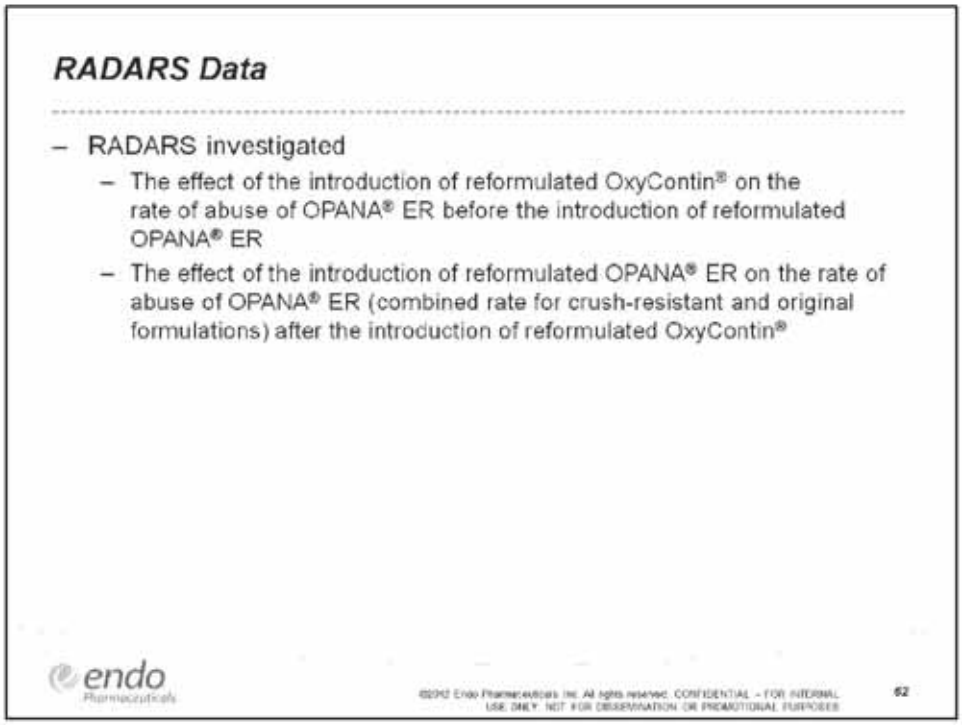
Description of RADARS System and streams of information we have available to us.



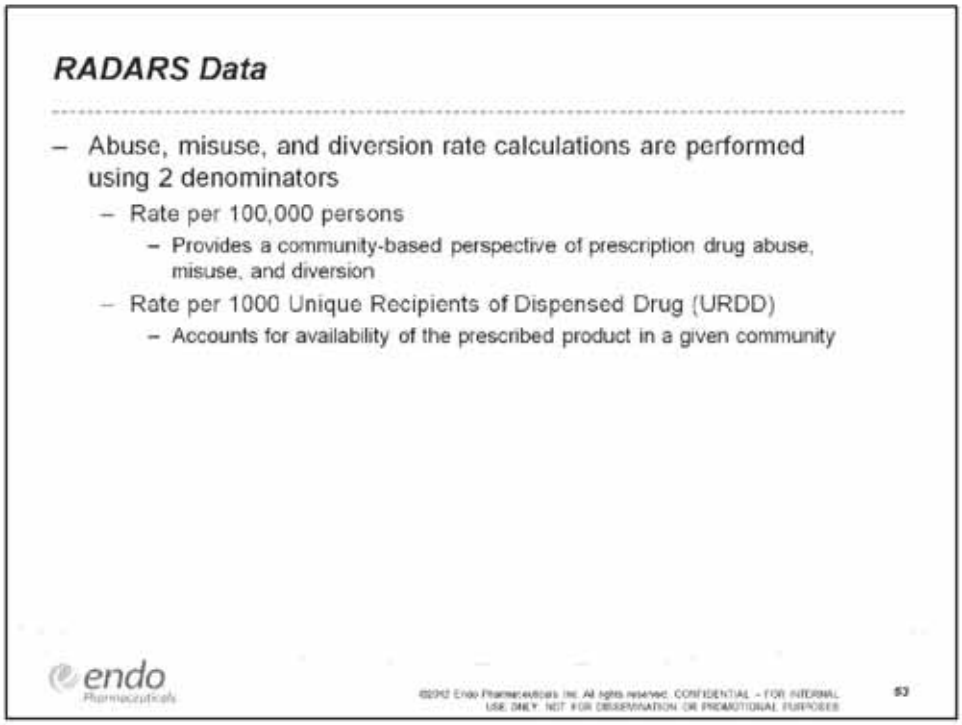
RADARS Poison Control Center coverage. You might not need this slide.



RADARS Drug Diversion Investigator coverage. You might not need this slide.



How RADARS present their data. Very important to understand.



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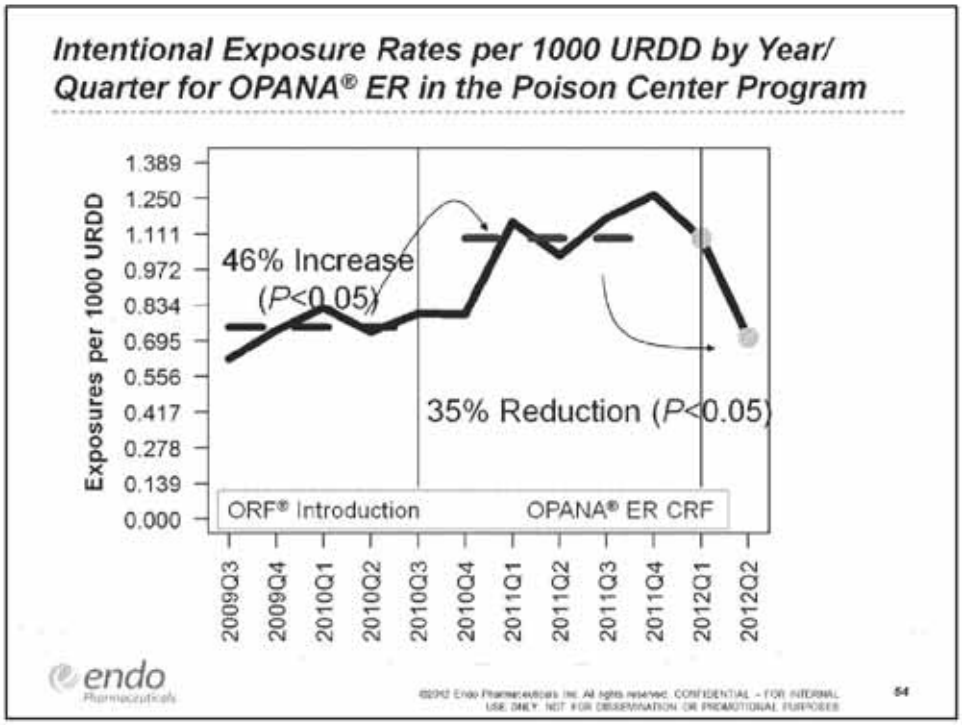
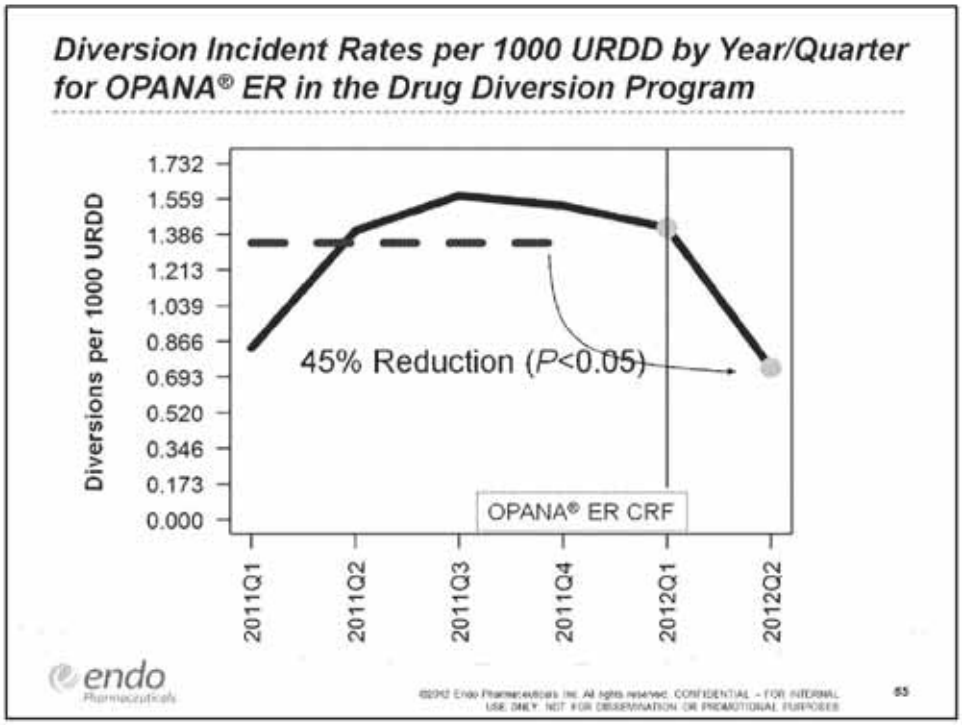
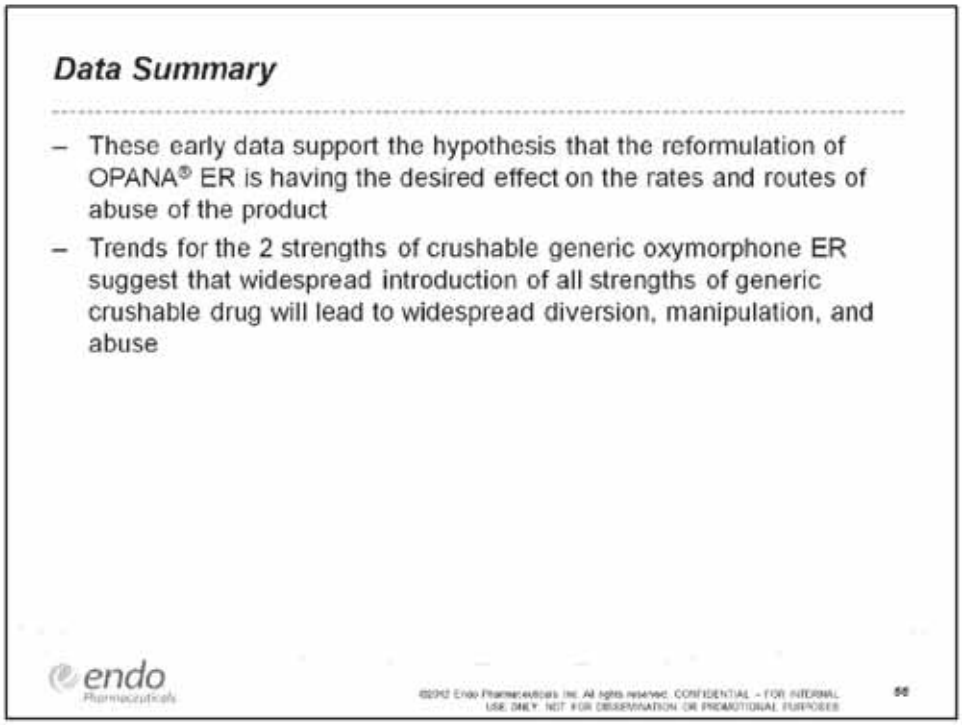


Poison Control Center data before and after introduction of OxyContin reformulation (ORF) and Opana ER reformulation. Horizontal lines represent average level of abuse during indicated time periods. This denominator is **URDD**.



RADARS Drug Diversion data are not available as far back as poison control center data. Horizontal line represents average number of diversion incidents over indicated time period. The denominator is **URDD**.


Data Summary
– These early data support the hypothesis that the reformulation of OPANA® ER is having the desired effect on the rates and routes of abuse of the product
– Trends for the 2 strengths of crushable generic oxymorphone ER suggest that widespread introduction of all strengths of generic crushable drug will lead to widespread diversion, manipulation, and abuse
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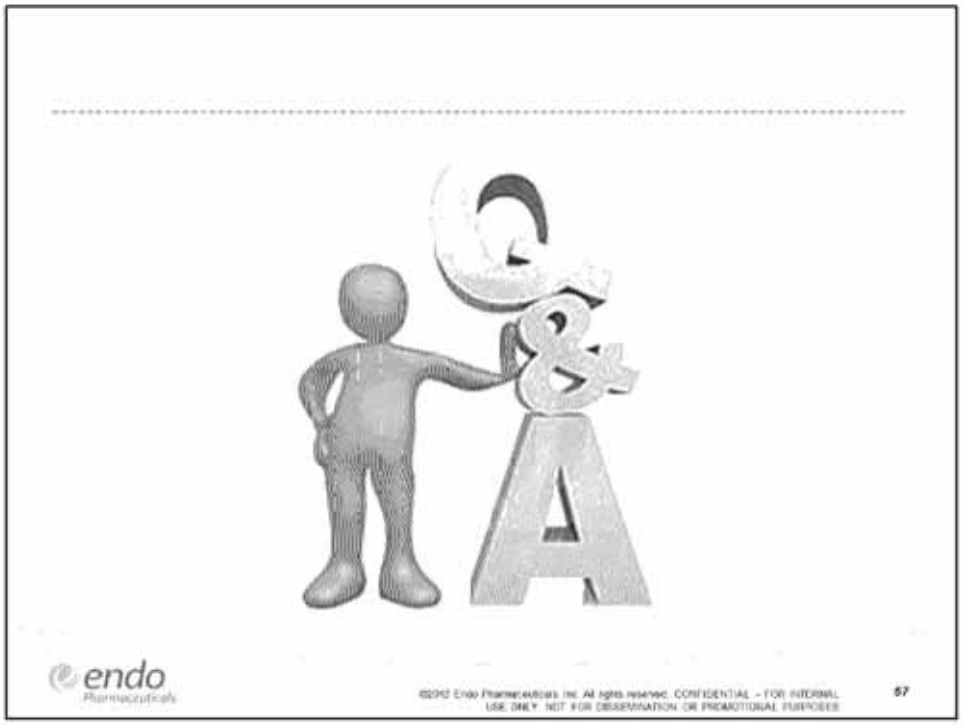
Summary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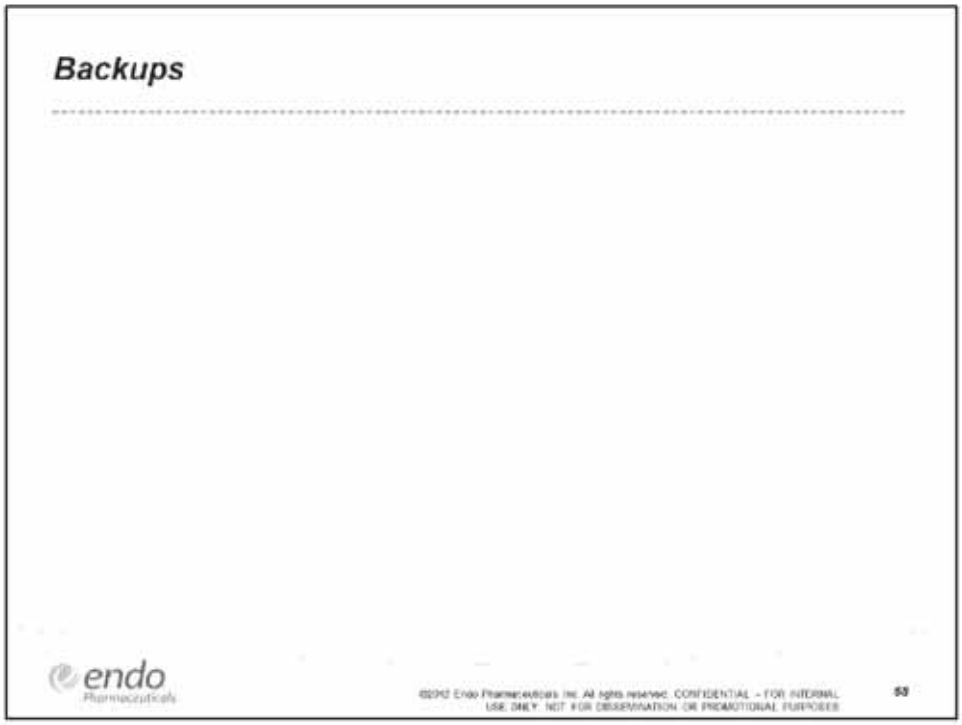
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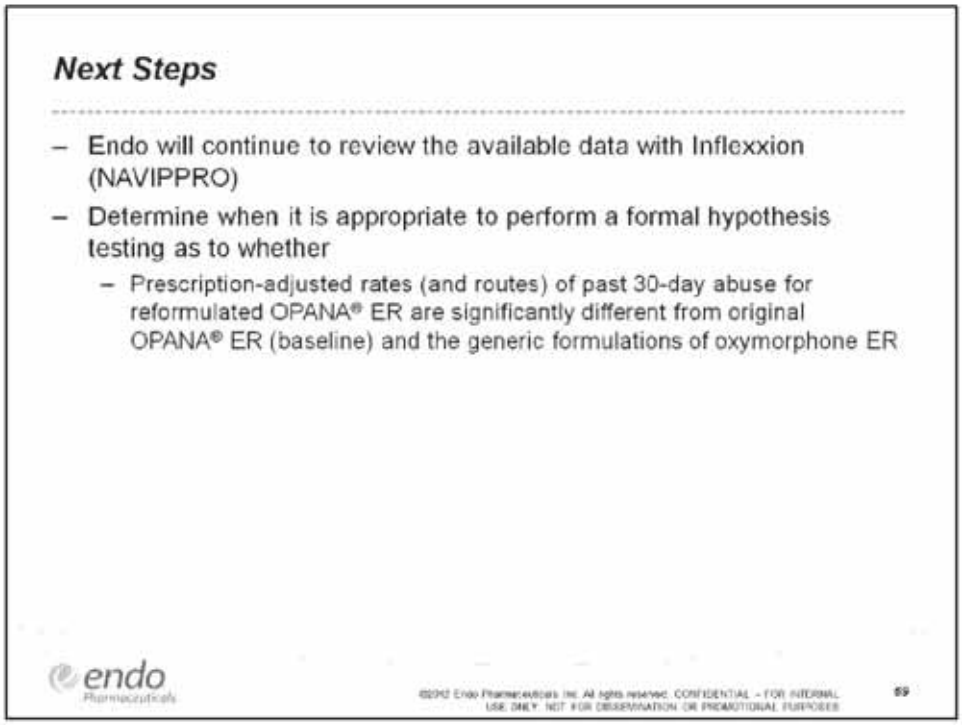
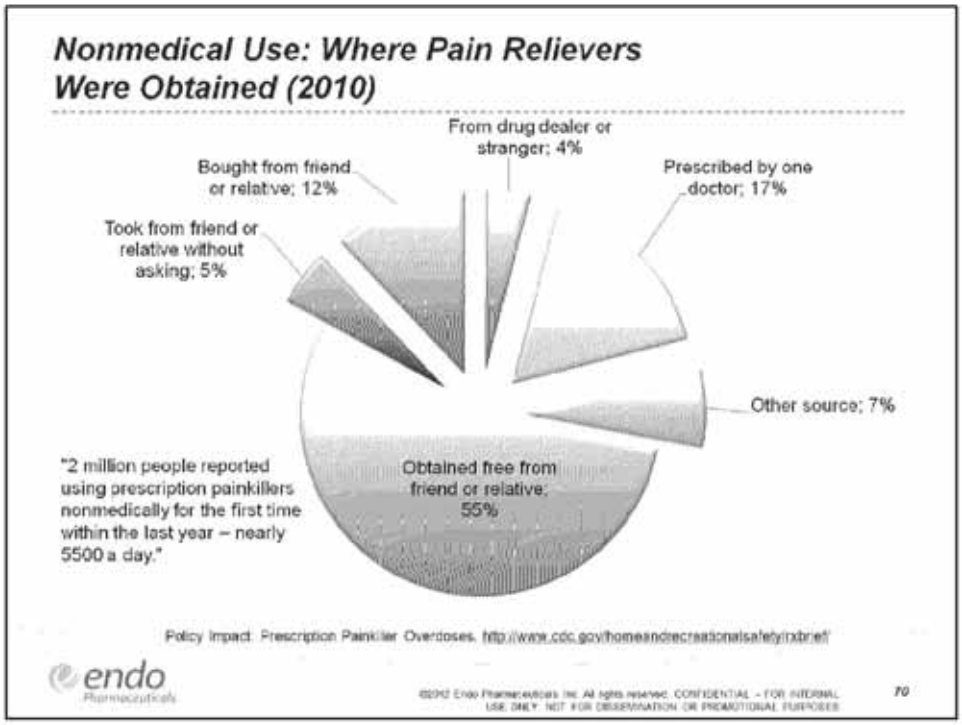


Limitations


Nonmedical Use: Where Pain Relievers Were Obtained (2010)
From drug dealer or stranger; 4%
Bought from friend or relative; 12%
Prescribed by one doctor; 17%
Took from friend or relative without asking; 5%
Other source; 7%
"2 million people reported using prescription painkillers nonmedically for the first time within the last year – nearly 5500 a day."
Obtained free from friend or relative; 55%
Policy Impact: Prescription Painkiller Overdoses. http://www.cdc.gov/homeandrecreationalsafety/rxbrief/
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NAVIPPRO Data Summarizes

- Past 30-day abuse of reformulated OPANA® ER and selected comparators as rates based on
  1. The total ASI-MV sample tracking reformulated OPANA® ER
  2. The subset of the ASI-MV sample tracking reformulated OPANA® ER and reporting prescription opioid abuse
  3. The total number of prescriptions dispensed
- Distribution of routes of administration reported by individuals within the ASI-MV network who indicated past 30-day abuse of reformulated OPANA® ER and comparators

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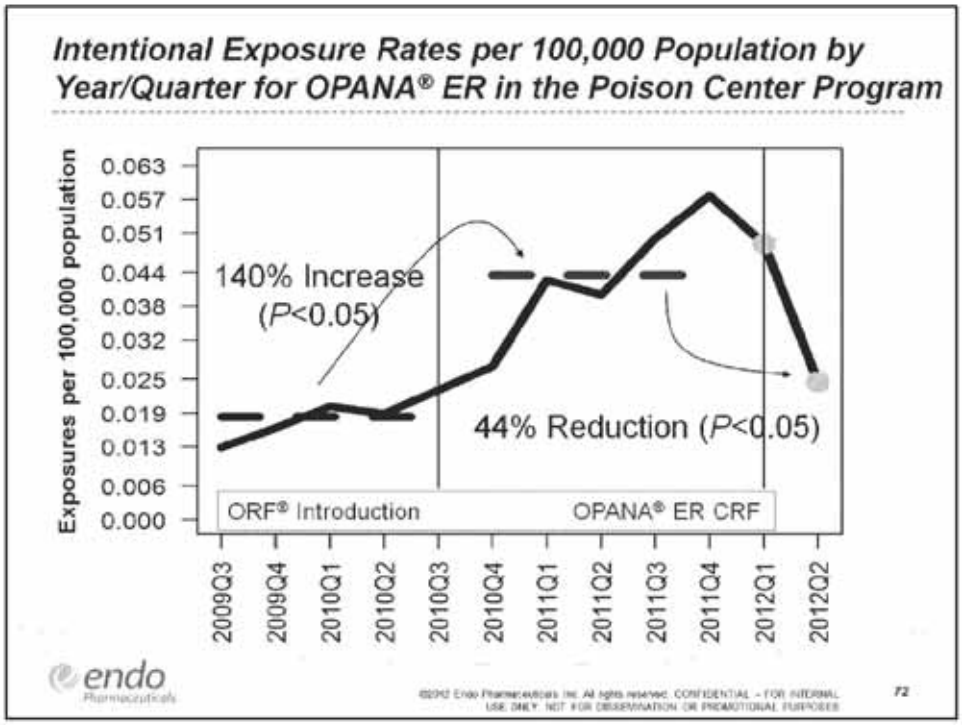
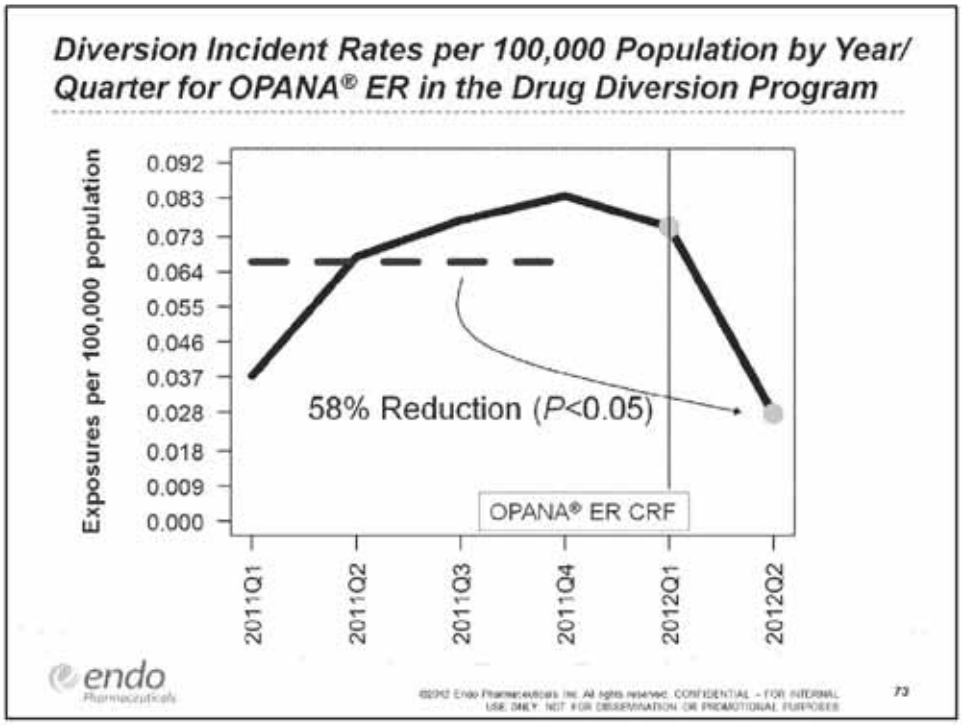


Poison Control Center data before and after introduction of OxyContin reformulation (ORF) and Opana ER reformulation. Horizontal lines represent average level of abuse during indicated time periods. This denominator is **population**.



RADARS Drug Diversion data are not available as far back as poison control center data. Horizontal line represents average number of diversion incidents over indicated time period. The denominator is **population**.

Discussion:
Oxymorphone ER Epidemiology of Abuse Data

- What has been the impact of the introduction of tamper-resistant formulations on your use of chronic opioid therapy?
- Has the presentation of aberrant drug behavior changed as a result of the introduction of tamper-resistant formulations?
  - If so, what do practitioners need to look for in these patients?
- What strategies do you use to identify high-risk patients?

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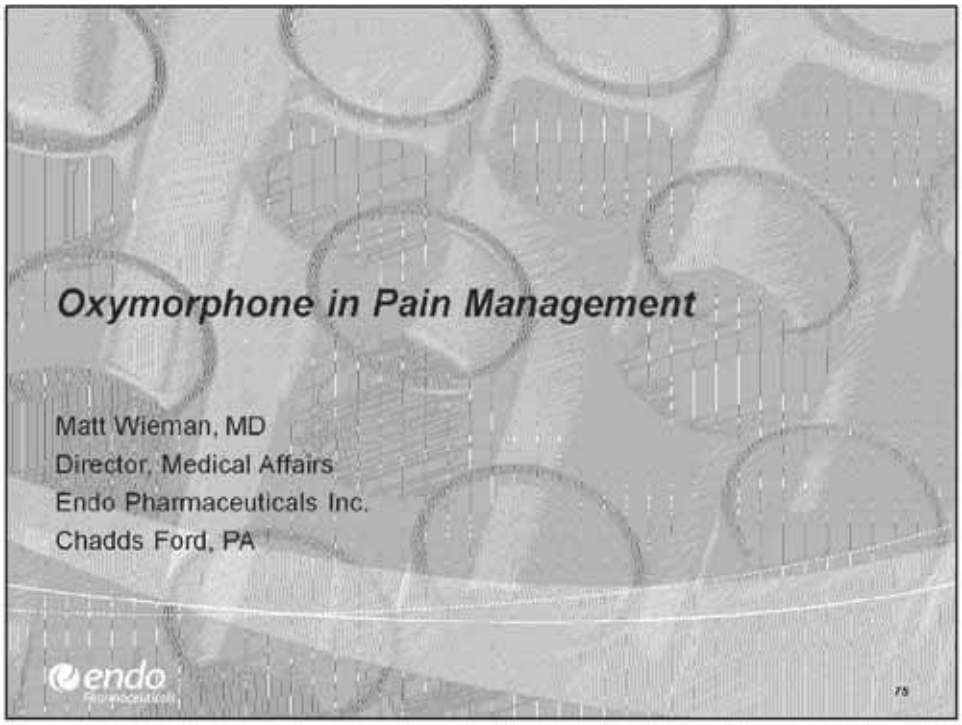

Discussion:
Oxymorphone in Chronic Pain Management

- How does oxymorphone fit into your chronic pain management armamentarium?
  - Typical patients
  - Disease states
  - Care settings

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Discussion:
Oxymorphone in Chronic Pain Management

- What knowledge gaps need to be addressed for prescribers to give adequate consideration to oxymorphone when it may be a suitable option for management of acute or chronic pain?
  - Pharmacology and formulations
  - Safety/efficacy in specific disease states or populations
  - Other considerations

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Discussion:
Oxymorphone in Chronic Pain Management

- What are potential barriers to oxymorphone selection?
  - Lack of familiarity, modeling, or mentoring by speciality
  - Availability and coverage of formulations
  - Patient concerns

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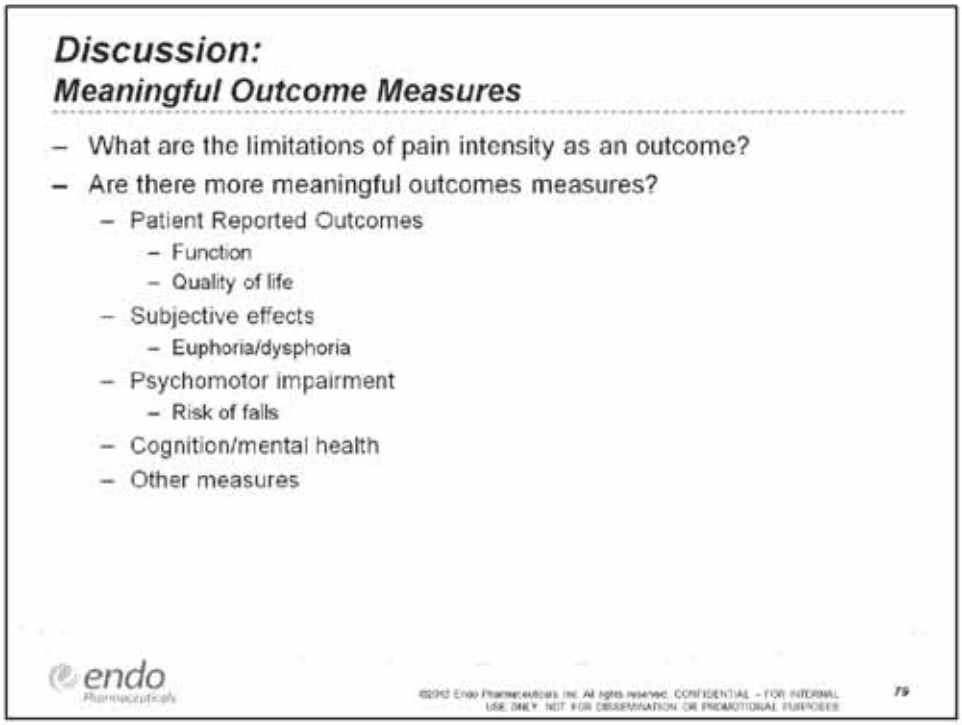

As Endo develops clinical study protocols, what are the most meaningful outcome measures we should include?

Knowledge Gaps in Specific Areas

- Do you believe there are knowledge gaps or a need for further research in these areas?
  - Oxymorphone at high doses (>180 mg/d morphine equivalent)
  - Value of ER TRF – need for IR TRF
  - Use in cancer pain
  - Use in specific disease states
  - Use in nociceptive vs. neuropathic pain
  - Subjective effects and cognitive/psychomotor effects
  - Continuum of care
    - Value of multiple formulations
    - Potential value of additional formulations (eg, oral liquid)

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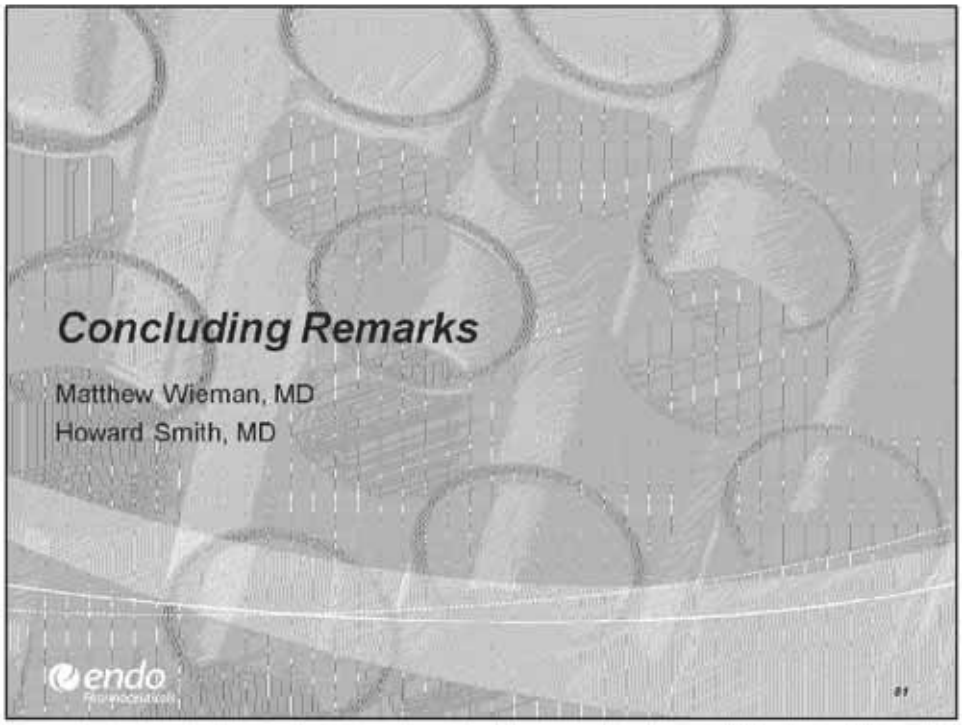
Concluding Remarks
Matthew Wieman, MD
Howard Smith, MD
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